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Influence of Intradialytic Aerobic Training in Cerebral Blood Flow and Cognitive Function in Patients with Chronic Kidney Disease: A Pilot Randomized Controlled Trial

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Keywords

Chronic kidney disease · Physical activity · Cerebral arteries · Cognition · Hemodialysis

Abstract

Background and Objectives: Changes in cerebral blood flow may play an important role in cognitive impairment among hemodialysis (HD) patients. Physical activity has a promising role in delaying cognitive impairment in general population, but there are only a few studies in HD to confirm this finding. We aimed to evaluate the effects of intradialytic aerobic training on cerebral blood flow and cognitive impairment in HD. ***Design, Setting, Participants, and Measurements:*** This is a pilot, controlled, randomized trial. Fifteen patients underwent intradialytic aerobic training 3 times a week for 4 months. The control group was comprised of another 15 patients. ***Results:*** Trained patients had a statistically significant improvement of cognitive impairment and basilar maximum blood flow velocity. The proportion of arteries with increased flow velocity was statistically significant between groups. ***Conclusions:*** Intradialytic aerobic training improves cognitive impairment and cerebral blood flow of patients in HD, suggesting a possible mechanism improving cognitive impairment by physical training in HD. These data still need to be confirmed by major trials.

Introduction

Chronic kidney disease (CKD) is an independent risk factor for cognitive impairment (CI) [1–4]. The prevalence of this condition among hemodialysis (HD) patients is up to 60% [2, 5]. Mechanisms involved in the etiology of CI in CKD are not completely understood. Uremic toxins may play a role. However, CI persistence, despite adequate dialysis, indicates that other factors contribute to brain dysfunction. Cerebrovascular disease is a major risk factor for CI both among the general population and CKD patients

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[6–8]. Considering the high prevalence of cardiovascular and cerebrovascular disease in CKD, CI in these patients may be mediated by impaired microcirculation [9–13].

CKD patients present high rates of physical inactivity [14] and low aerobic capacity [15, 16]. Furthermore, physical activity (PA) is reputable as a new therapeutic strategy to CI. There is an association between PA high levels and higher cognitive ability [17]. In healthy adults, there is an association between high cerebral blood flow and aerobic exercise [18]. Aerobic exercise induces an increase in cerebral blood flow in stroke animals and patients [13, 19, 20].

Studies have shown the importance of lifestyle modification as an intradialytic PA program and as an adjuvant in CKD treatment [21]. There are several studies evaluating PA in CKD; others reporting CI observed in these patients. However, there are no studies evaluating the relationship of those important variables with cerebral hemodynamics. Therefore, we investigated the effects of intradialytic aerobic training on cerebral blood flow and cognitive function in HD patients.

Materials and Methods

This was a pilot, randomized, controlled trial with physiotherapy intervention and intention-to-treat analysis. The intervention group (IG) was submitted to intradialytic aerobic exercise 3 times a week for 4 months. The control group (CG) was managed with usual care. Patients underwent treadmill test, evaluation of cerebral blood flow, and cognitive function test at random and after 4 months. Baseline assessments were performed within 2 weeks prior to the training protocol initiation, and post-intervention assessments were performed no later than 2 weeks after the protocol ending. All the assessments were performed on non-dialysis days. Patients' randomization was performed using SAS for Windows version 9.3 using PLAN procedure for a completely randomized design for 2 groups of 20 patients each. This study was performed from June 2012 to December 2014.

CKD patients from a single center, regardless of etiology, on maintenance HD for at least 3 months, older than 18 years, stable medication and no contraindications to perform PA were enrolled in this study.

Exclusion criteria were previous coronary artery disease diagnosis, previous positive stress test for cardiac ischemia, patients classified as active or very active, patient who had experienced stroke, acute or chronic infection in activity, stage II hypertension (≥160 mm Hg systolic or ≥100 mm Hg diastolic), and previous diagnosis of neoplasia, dementia, delirium, or presence of depression and medications for cognitive function use.

Initial Assessment

Patients underwent standardized clinical evaluation based on the following parameters: age, gender, education level, CKD etiology, race, HD vintage, presence of diabetes mellitus, smoking status, and body mass index. All data were recorded on an individual assessment form.

Physical Activity Level

International Physical Activity Questionnaire was used to measure PA level. Individuals were classified as very active, active, irregularly active, or sedentary [22, 23].

Cognitive Function

The instrument used for CI screening was the Mini Mental State Examination (MMSE). It is divided into questions assessing specific cognitive functions: temporal and space orientation, immediate memory, calculation, words recall, language, and visual construction, with a score ranging from 0 to 30 [24–26].

Transcranial Doppler

The equipment used was portable 2 MHz transducers Doppler Box (DWL Electronic Systems, Germany), pulsed, gains ranging from 31 to 44 MHz, sample volume 8–12, color M-mode and audio record in all exams, 200 Gates per channel. This examination allows dynamic assessment of the major intracranial arteries blood circulation with 2 MHz transducer. The transducer was set in the temporal bone above the zygomatic arch, and the middle cerebral artery (MCA) M1 portion was evaluated at a depth and direction determined by the Circle Willis map. Breath Holding Index (BHI) was collected at the MCA insonation time and the average velocity after 4 s of continuous signal at the screen was registered. This record is the resting average velocity (RAV). After this, the patient was oriented about apnea. The average velocity at the time before the end of the apnea period (apnea average velocity – AAV) and total apnea time (TAT) were registered. Then, the patient was requested to induce hyperventilation for 2 minutes, breathing in deeply and frequently. At the end of this time, average velocity was registered (average velocity – in hyperventilation – AVH). If there was carotid stenosis, the test was performed bilaterally. If not, the test was performed in the side with the best acoustic window. With these values, BHI was estimated using the following formula: BHI: $([(AAV - AVH)/RAV]/TAT) \times 100$. The result was expressed in % seconds, and the normal value was 1.2 ± 0.6% s. BHI <0.69% seconds is classified as impaired cerebral vasoreactivity [27, 28]. This test also allows indirect evaluation intracranial resistance to blood flow by pulsatility index (PI), which is estimated by the following formula: $PI = PSFR - FDFR/PSFR$. PSFR corresponds to the peak systolic flow rate and FDFR corresponds to final diastolic flow rate. PI normal values are between 0.6 and 1.0 [28]. The neurologists, who conducted transcranial Doppler (TCD), were blind to patient's allocation in intervention or CG. They did not take part in exercise training during HD sessions.

Exercise Test

Exercise test ET was carried out on the basis of Brazilian Society of Cardiology guidelines. The test was performed on a treadmill with electrocardiographic, blood pressure (BP), and subjective feeling of tiredness monitoring. Bruce protocol was used for all evaluations, which comprises progressive increases of treadmill speed and inclination every 3 min. All patients were instructed to use their medication as usual. ET was stopped in cases of BP and heart rate (HR) atypical changes, chest discomfort clinical manifestations, disproportional dyspnea according to the efforts intensity, and significant changes in electrocardiogram [29].

Table 1. Comparison of demographic and clinical baseline data of the intervention group and the control group (n = 30)

Characteristic	IG (n = 15)	CG (n = 15)	p value
Gender, male, n (%)	7 (46.6)	8 (53.3)	0.72
Age, years	50.3±17.24	57.8±15.01	0.09
Schooling, years	5.7±3.58	4.7±3.98	0.43
Smoking, n (%)	5 (33.3)	3 (20.0)	0.43
Hemodialysis vintage, months	26.0±14.58	21.1±27.10	0.32
Diabetes, n (%)	3 (20.0)	6 (40.0)	0.16
Arterial hypertension, n (%)	13 (86.6)	12 (80.0)	0.94
BMI, kg/cm^2	25.7±5.64	26.6±4.60	0.55
Antihypertensive medication, n (%)			
Diuretics	5 (33.3)	6 (40)	0.70
Calcium channel blockers	4 (26.6)	8 (53.3)	0.13
Beta blockers	9 (60)	10 (66.6)	0.70
ACE inhibitors or ARBs	10 (66.6)	9 (60)	0.71
Sympatholytic	2 (13.3)	4 (26.6)	0.36
Vasodilators	0 (0)	1 (6.6)	0.31
Etiology of CKD, n (%)			
Hypertension	6 (40.0)	5 (33.3)	
Diabetic nephropathy	3 (20.0)	5 (33.3)	0.34
Glomerular diseases	4 (26.6)	4 (26.6)	
Other causes	2 (13.4)	1 (6.6)	

Data are expressed as mean ± SD or , n (%).
GI, intervention group; GC, control group; BMI, body mass index; ACE, angiotensin-converting enzymes; ARB, angiotensin II receptor blockers; CKD, chronic kidney disease.

Physical Training Program

Only IG was subjected to physical training program, which was performed during the first 2 h of HD sessions, 3 times a week. The protocol lasted for 4 months. PA was composed by global stretching and aerobic training in cycle ergometer (Foot Hand Bike Brand – Polimet®) adapted to hospital situation. Aerobic training was performed for at least 30 min with training range 65–75% of maximum HR, controlled by Polar heart monitor FS3C®. HR target was determined by ET. Aerobic training time has been increased progressively, as the patient evolution, until it reaches 45 min.

Data Analysis

Sample Size Calculation

To detect a difference of 10 cm/s in MCA flow, estimating an SD of the difference of 15 cm/s and an alpha error 0.05 and beta error 0.10, the estimated sample size was 20 patients in IG and as many in CG. Thus, the calculation of total sample size was 40 patients.

Statistical Analysis

For comparisons between groups, times, and interactions between groups and moments, 2-way analysis of variance for repeated measures was used followed by Tukey test for data with normal distribution. For data with asymmetric distribution, the same design was used by setting a generalized linear model with gamma distribution followed by multiple comparison test of Wald. Poisson regression was performed to test the proportion of vessels of improving in cerebral blood flow. Statistical significance was set at $p < 0.05$. Data were presented as mean ± SD. Statistical programs used for analysis were SigmaStat for Windows version 3.5 (Systat Software Inc., CA, USA) and Statistical Analysis System (version 9.3).

Results

During the period of the research, 184 patients were on maintenance HD in the institution. Of these, 101 patients met some exclusion criteria and 48 patients had no interest in participating in the study. So, 35 patients were randomized into 2 groups, 17 subjects in IG and 18 subjects in CG. Two patients in IG were excluded before the end of the study because of kidney transplantation. In CG, 3 patients were excluded before the end of the study due to: kidney transplantation, bowel cancer, and consent removal. All these events occurred during the period between the first and second evaluation. Three patients in IG (20%) and 2 patients in CG (13.3%) did not undergo TCD because they had an unfavorable acoustic window for the exam.

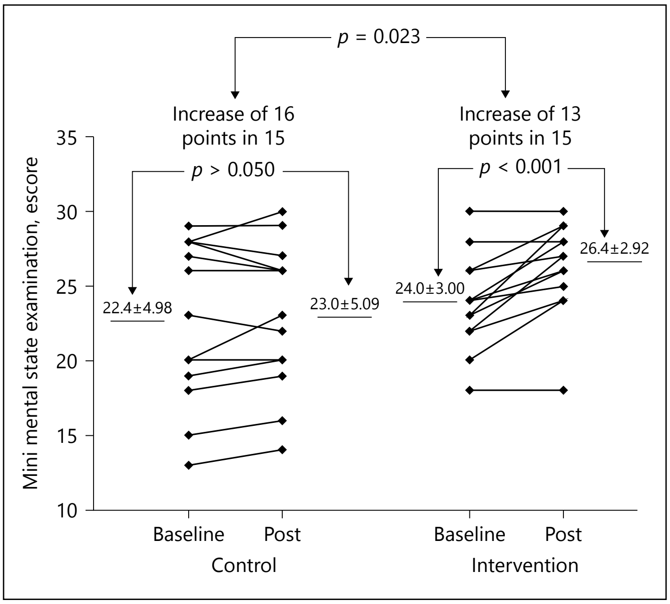

Fig. 1. The cognitive function of the control group (CG) and intervention group (IG) at different moments ($n = 30$).

Baseline demographic and clinical data were homogeneous between the 2 groups and did not change in the evaluation post intervention (Table 1). The variables interdialytic weight gain (IG: 2.9 ± 0.89 kg at baseline and 2.9 ± 0.78 kg at the ending/CG: 2.7 ± 0.88 kg at baseline and 2.7 ± 0.85 kg at the ending) and ultrafiltration volume (IG: 3.0 ± 0.75 L at baseline and 3.0 ± 0.79 L at the ending/CG: 2.6 ± 0.95 L at baseline and 2.6 ± 0.82 L at the ending) did not present statistically significant differences between groups, moments, and interaction among groups and moments. It is important to emphasize that the antihypertensive medication was not modified during the study.

According to the International Physical Activity Questionnaire, the PA level of 8 patients in IG was classified as irregularly active (53.4%) and 7 patients were considered sedentary (46.6%). In CG, 6 patients were classified as irregularly active (40%) and 9 patients were sedentary (60%). There was no statistical difference between the groups ($p = 0.35$).

The groups were homogeneous at baseline regarding cognitive function, ($p = 0.43$). After the intervention, there was a significant improvement in IG. IG MMSE initial average was 24.0 ± 3.00 points and 26.4 ± 2.92 at the end. CG average was 22.4 ± 4.98 points initially and 23.0 ± 5.09 at the end. Thus, there was an improvement in cognitive function, with a difference between times in IG ($p < 0.001$) and interaction between groups and time ($p = 0.001$). Figure 1 shows IG and CG changes in cognitive function at different times.

Cerebral blood flow was homogeneous between the groups at baseline regarding maximum and average blood flow velocity of all cerebral arteries evaluated bilaterally (MCA, anterior cerebral artery, posterior cerebral artery, vertebral artery); the basilar artery was also evaluated. PI and cerebral vasomotor reactivity test, which are represented by BHI, were also homogeneous at baseline. Basilar artery maximum blood flow velocity was different between groups ($p = 0.025$) and there is an interaction between groups and moments ($p = 0.029$). IG had an increase in basilar artery maximum blood flow velocity from 62.4 ± 17.93 to 81.2 ± 21.37 cm/s after intervention, while there was a decrease from 66.0 ± 21.67 to 51.5 ± 17.60 cm/s in CG. Comparison between IG and CG before and after the physical training program regarding cerebral blood flow is shown in Table 2.

We obtained numerical improvements in 9 areas assessed in cerebral hemodynamics in IG after physical training protocol. There was a numerical increase of maximum and average blood flow velocity of all assessed arteries in IG, except average right posterior cerebral artery flow velocity. However in CG, there was numerical improve only in 4 arteries and numerical decrease of maximum and average blood flow velocity of the other 5 evaluated cerebral arteries. The proportion of arteries in which there was a maximum and average cerebral blood flow velocity increase had a statistically significant difference between groups ($p = 0.002$ and $p = 0.038$ respectively), as shown in Figures 2 and 3. In Figure 2, each point represents the mean maximum velocity of each assessed artery. In Figure 3, each point represents the mean of average velocity of each artery that was assessed. Figures 2 and 3 represent graphically the values from Table 2, besides the frequency of territories that did not have any flow increase or decrease.

There was a PI increase of 7 areas in IG, while in CG there was no increase, with statistically significant difference in proportion between groups ($p = 0.015$), as shown in Figure 4.

Regarding ET variables, there were numerical improvements in VO2max, exam time, walked distance, and maximum MET in IG. However, there was no statistically significant difference between groups, between moments, and interaction between groups and moments. There is only a trend between times for VO2max ($p =$

Table 2. Comparison of the intervention group and the control group before and after the protocol of intradialytic aerobic exercise in relation to cerebral blood flow velocity measured by transcranial Doppler (*n* = 25)

Characteristic	Intervention group		Group control		P1	P2	P3
	baseline (*n* = 12)	post-intervention (*n* = 12)	baseline (*n* = 13)	post-intervention (*n* = 13)			
RMCA maximum, cm/s	95.3±36.14	101.9±21.18	86.4±19.59	95.2±28.52	0.424	0.293	0.876
RMCA mean, cm/s	60.0±24.53	62.4±15.62	57.9±17.23	63.9±21.40	0.960	0.378	0.699
IP RMCA	0.9±0.32	1.0±0.30	0.8±0.29	0.8±0.26	0.255	0.490	0.432
LMCA maximum, cm/s	104.5±28.95	104.6±32.96	90.3±17.58	96.0±18.26	0.267	0.575	0.587
LMCA mean, cm/s	65.2±15.40	67.3±19.24	58.6±11.87	64.4±15.82	0.279	0.635	0.600
IP LMCA	0.9±0.29	0.9±0.22	0.9±0.28	0.8±0.25	0.610	0.189	0.536
RACA maximum, cm/s	74.0±22.66	93.3±14.36	79.6±17.79	73.5±19.52	0.222	0.312	0.060
RACA mean, cm/s	46.0±16.29	53.9±13.49	49.6±13.77	50.4±15.45	0.992	0.301	0.394
IP RACA	1.1±0.42	1.2±0.51	1.0±0.34	0.8±0.24	0.147	0.399	0.131
LACA maximum, cm/s	72.0±20.18	76.5±20.71	75.4±21.72	82.2±21.44	0.557	0.286	0.830
LACA mean, cm/s	44.5±14.53	46.6±14.18	49.7±15.38	55.4±15.05	0.227	0.245	0.585
IP LACA	1.1±0.47	1.1±0.30	1.0±0.31	0.9±0.34	0.242	0.427	0.621
RPCA maximum, cm/s	59.6±16.90	61.6±15.06	54.1±12.74	58.1±20.73	0.461	0.465	0.806
RPCA mean, cm/s	35.8±11.16	34.5±11.84	33.6±12.08	34.9±11.85	0.840	0.995	0.587
IP RPCA	1.1±0.42	1.3±0.64	1.2±0.96	1.0±0.39	0.718	0.940	0.127
LPCA maximum, cm/s	47.5±14.77	60.2±21.19	56.3±18.83	50.5±14.39	0.934	0.471	0.064
LPCA mean, cm/s	29.3±8.57	33.0±7.22	33.7±10.79	32.5±11.25	0.580	0.618	0.335
IP LPCA	1.0±0.46	1.2±0.46	1.1±0.43	0.9±0.35	0.613	0.652	0.062
RVA maximum, cm/s	49.5±26.78	69.2±19.97	57.0±23.15	50.0±16.26	0.439	0.358	0.063
RVA mean, cm/s	30.6±17.26	32.7±10.47	33.4±12.30	28.4±10.01	0.869	0.658	0.283
IP RVA	1.2±0.33	1.7±0.54	1.3±0.92	1.1±0.47	0.531	0.320	0.212
LVA maximum, cm/s	52.7±22.79	66.6±24.82	50.6±19.76	45.2±14.61	0.123	0.454	0.099
LVA mean, cm/s	30.9±14.21	31.2±14.97	29.2±12.81	26.8±10.16	0.553	0.711	0.616
IP LVA	1.3±0.51	2.0±1.00	1.4±1.02	1.1±0.55	0.098	0.361	0.094
Basilar artery maximum, cm/s	62.4±17.93[a, A]	81.2±21.37[b, A]	66.0±21.67[a, A]	51.5±17.60[a, B]	0.025	0.763	0.029
Basilar artery mean, cm/s	36.3±13.14	43.9±14.28	39.7±17.77	31.4±13.58	0.363	0.939	0.093
IP Basilar artery	1.1±0.27	1.4±0.43	1.3±0.65	1.1±0.60	0.883	0.713	0.173
Breath Holding Index (% seg)*	1.5±0.64	1.4±0.64	1.2±0.80	1.2±0.75	0.301	0.928	0.887

Data are expressed as mean ± SD. Values indicate the maximum and mean velocity of cerebral blood flow in the respective artery.

P1, comparison between groups; P2, comparison between moments; P3, interaction between groups and moments. IP, pulsatility index; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; RACA, right anterior cerebral artery; LACA, left anterior cerebral artery; RPCA, right posterior cerebral artery; LPCA, left posterior cerebral artery; RVA, right vertebral artery; LVA, left vertebral artery.

* Cerebral vasomotor reactivity test. [a, b] Values followed by the same lowercase letter. Setting up groups. Do not differ at the 5% level by the Wald test. [A, B] Values followed by the same capital letter. Setting moments. Do not differ at the 5% level by the Wald test.

0.06). Maximum and resting HR were not different between groups, between moments, and interaction between groups and times (Table 3).

Discussion

The beneficial effects of intradialytic exercise are already known in HD patients. However, there are no studies evaluating the effect of intradialytic aerobic exercise in cerebral hemodynamics and cognitive function in HD patients. Thus, the primary objective of this study was to determine, through a randomized controlled clinical trial, the effect of an intradialytic aerobic training program on these parameters. It was observed that intradialytic aerobic exercise for 16 weeks resulted in cognitive function improvement.

The MMSE, which was used for cognitive function assessment, has been widely applied for cognitive screening and its accuracy depends on age and educational level. In this study, age and education level were similar in both groups.

In healthy subjects, a meta-analysis showed a positive association between PA and cognitive function improve-

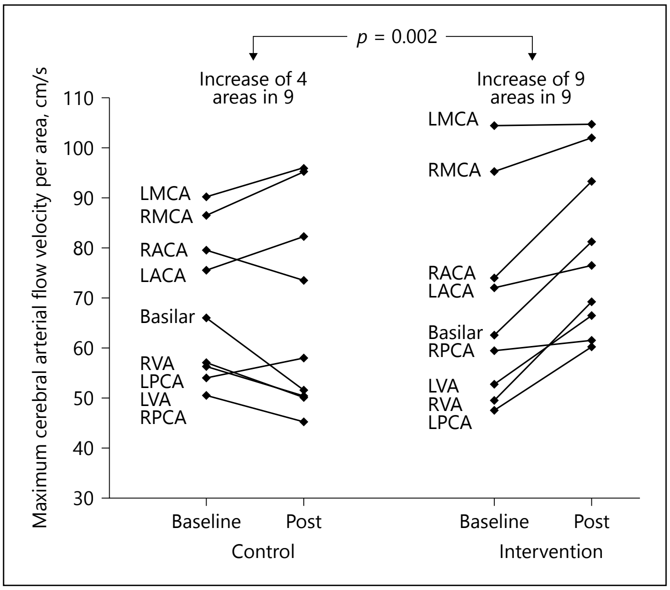

Fig. 2. The maximum cerebral artery flow velocity of the CG and IG at different moments ($n = 25$). CG, control group; IG, intervention group; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; RACA, right anterior cerebral artery; LACA, left anterior cerebral artery; RPCA, right posterior cerebral artery; LPCA, left posterior cerebral artery; RVA, right vertebral artery; LVA, left vertebral artery.

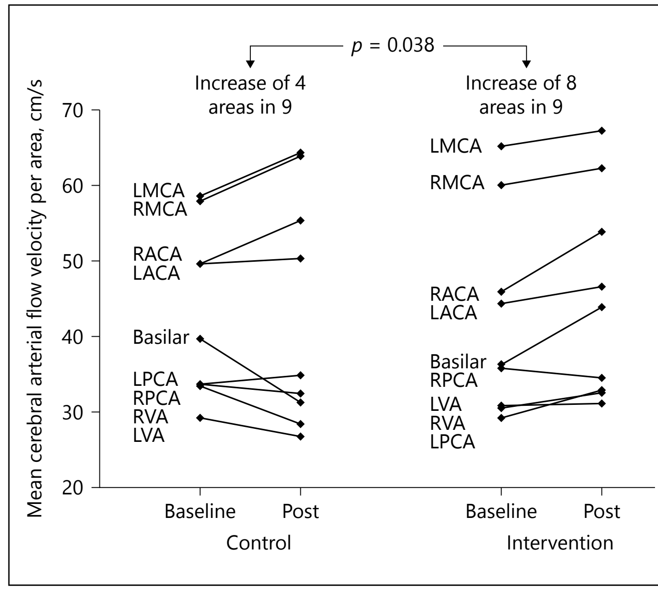

Fig. 3. The mean cerebral arterial flow velocity of the CG and IG at the different moments ($n = 25$). CG, control group; IG, intervention group; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; RACA, right anterior cerebral artery; LACA, left anterior cerebral artery; RPCA, right posterior cerebral artery; LPCA, left posterior cerebral artery; RVA, right vertebral artery; LVA, left vertebral artery.

ment [30]. The prophylactic effect of PA in brain health, CI, and dementia risk in healthy subjects have been shown, especially among the elderly [31–33]. Moreover, elderly participants of a PA program had a lower risk of cerebrovascular and cardiovascular disease [34]. Therefore, literature reports that PA may have implications in CI prevention and risk for brain impairment seems to be inversely proportional to the amount of PA practiced throughout life [35].

Several physiological mechanisms could explain the beneficial effect of PA on cognitive function, and increased cerebral blood flow. Main mechanisms proposed to explain the neuroprotective effect of exercise are cardiovascular, immune, and neurotrophic signaling [36]. Immunological and neurotrophic signaling were not evaluated in this study.

Cardiovascular benefits of PA, which are clearly elucidated in literature, are essential for the small vessel condition improvement [37, 38], increased cerebral blood flow, and nutrient delivery, thereby helping to optimize brain health [39]. Acute exercise increases cardiac output in response to increase in oxygen and energy substrates consumption compared to the resting state, which increases cerebral blood flow [40]. This in-

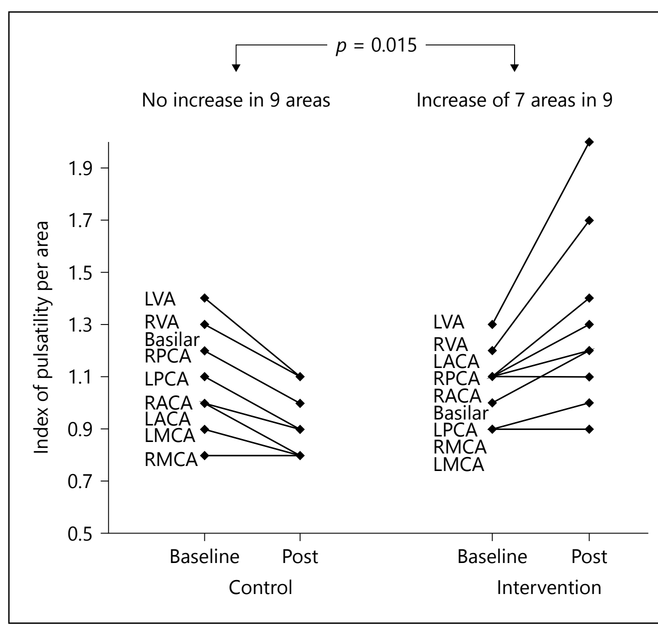

Fig. 4. The pulsatility index of the CG and IG at different moments ($n = 25$). CG, control group; IG, intervention group; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; RACA, right anterior cerebral artery; LACA, left anterior cerebral artery; RPCA, right posterior cerebral artery; LPCA, left posterior cerebral artery; RVA, right vertebral artery; LVA, left vertebral artery.

Table 3. Comparison of the intervention group and the control group before and after the protocol of intradialytic aerobic exercise in relation to the parameters of the ergometric test (*n* = 30)

Characteristic	Intervention group		Group control		P1	P2	P3
	baseline (*n* = 15)	post-intervention (*n* = 15)	baseline (*n* = 15)	post-intervention (*n* = 15)			
VO2max, mL/kg min	29.2±9.16	31.3±8.36	23.3±10.74	24.6±10.77	0.098	0.060	0.638
Exam time, min	7.7±2.86	8.7±2.48	6.2±3.06	6.6±3.05	0.077	0.065	0.610
Distance, m	547.1±272.25	606.5±258.64	397.7±251.86	426.7±261.58	0.105	0.061	0.507
MET maximum	8.3±2.62	8.9±2.39	6.6±3.07	7.0±3.08	0.096	0.057	0.623
HR maximum, bpm	149.3±19.94	146.5±25.93	142.4±30.50	137.8±21.53	0.376	0.386	0.830
HR resting, bpm	75.0±10.63	77.8±17.43	75.2±9.16	74.8±10.87	0.757	0.785	0.686

Data are expressed as mean ± SD.

P1, comparison between groups; P2, comparison between moments; P3, interaction between groups and moments; VO2max, maximum oxygen consumption; HR, heart rate.

crease in cerebral blood flow triggers several neurobiological mechanisms in the brain tissue. Repeated and regular neurobiological changes are related to brain tissue synthesis by increasing angiogenesis, neurogenesis, synaptogenesis, and neurotransmitters synthesis in different brain structures involved in cognition [41, 42].

In the current study, after PA intervention, there was a consistent numerical improvement in maximum and average blood flow velocity of the 9 evaluated cerebral arteries in IG, while only 4 improved and 5 worsened in CG. There was a statistically significant difference between these proportions. Ainslie et al. [18] showed the first evidence of association of improvement in cerebral blood flow velocity in MCA induced by regular aerobic exercise in healthy men. Subsequently, a study with patients who had experienced stroke reported improvements in cerebral blood flow parameters also induced by aerobic exercise [13].

Regarding cerebral blood flow, there was significant increase in maximum velocity on basilar artery in IG, after PA intervention. There are no reports in literature about the PA-positive effect especially on the basilar artery blood flow. Basilar trunk is responsible for hippocampus vascularization, which is associated with cognitive function, mainly the memory [43]. With aging, there is a decrease in this region, leading to impaired memory and increased risk of dementia. PA may improve hippocampus perfusion, with anatomical and physiological changes, contributing with the CI decrease [43, 44]. Similarly, other studies with healthy elderly have demonstrated an association between PA and increase in hippocampal volume [45].

In the present study, there was no association between PA and cerebral vasoreactivity, represented by BHI. However, participants showed no impairment of this variable at baseline (IG: 1.5 ± 0.64 and CG: 1.4 ± 0.64). This may be the determining fact to not find an association. Murrell et al. [46] evaluated the effect of age and 12-week aerobic training on cerebral blood flow and cerebral vasoreactivity at rest and during submaximal exercise, and observed increase in cerebrovascular reactivity to hypercapnia. This increase was induced by improvement in physical fitness, independent of age and possibly associated with increased blood flow velocity in MCA at rest. These results suggest that physical exercise is a therapeutic tool for cerebrovascular disease prevention. A study, which determined the effect of PA program on brain vasoreactivity in the elderly, reported improvement on cerebral hemodynamic response in IG, as well as BP parameters, serum cholesterol, and triglyceride levels [47].

In this study, an increase in PI of 7 areas in IG was observed, while there was no increase in CG, with a statistically significant difference in proportion between groups. PI is used for indirect evaluation of intracranial cerebral blood flow resistance. Higher the flow resistance, lower the diastolic velocity of blood flow velocity spectrum and hence, a higher value of PI [28].

Data obtained from evaluation of the same participants of the current study and not presented (personal communication Viviana Rugolo Oliveira Silva) show improvement in left ventricular hypertrophy, as well as improvement in flow-mediated vasodilation test in IG after the intradialytic aerobic training protocol. These results show vascular improvement in other areas, which usually are associated with cerebral circulation improvement.

Some limitations of this work should be recognized. The sample size did not reach 20 patients in each group, which may have reduced statistical power. Nevertheless, all patients in IG completed the protocol. There was only a numerical increase in aerobic capacity in IG. This may have occurred, since VO2 was not directly measured but was estimated. Another limitation was the lack of temporal acoustic window for the TCD completion in some patients in both groups. However, these findings are consistent with a study that indicates acoustic temporal window absence in 20% of evaluated individuals, related to female gender, advanced age, and African and Asian ethnic [48].

The current study strength is that it is the first one demonstrating the beneficial effect of intradialytic aerobic exercise training on cognitive function and cerebral blood flow in maintenance HD patients in a randomized controlled clinical trial.

Conclusion

The intradialytic aerobic exercise protocol was beneficial for cognitive function improvement in patients on HD. The intradialytic aerobic exercise had a positive effect on cerebral blood flow, increasing maximum and average blood flow velocity in most of the evaluated arteries, suggesting a possible mechanism for cognitive function improvement. Moreover, this intradialytic aerobic exercise protocol was effective and safe.

In this way, the current study provides evidence for the implementation of intradialytic exercise programs in the HD unit routine, and may play a supporting role in CKD treatment. Major trials are still needed to confirm these results.

Ethics Statement

Written informed consent was obtained from all subjects. This study was approved by the Ethics Research Committee (number 4024-2011) and meets ethical guidelines with 146/06 Brazilian National Health Resolution and registered in Brazilian Clinical Assays Register (REBEC number RBR-33t6zm).

Disclosure Statement

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

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References

1 Etgen T, Chonchol M, Förstl H, Sander D: Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. Am J Nephrol 2012;35:474–482.
2 Kurella Tamura M, Xie D, Yaffe K, Cohen DL, Teal V, Kasner SE, et al: Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. Clin J Am Soc Nephrol 2011;6:248–256.
3 Yaffe K, Ackerson L, Kurella Tamura M, Le Blanc P, Kusek JW, Sehgal AR, et al; Chronic Renal Insufficiency Cohort Investigators: chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. J Am Geriatr Soc 2010;58:338–345.
4 Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, et al: Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis 2008;52:227–234.
5 Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, et al: Cognitive impairment in hemodialysis patients is common. Neurology 2006;67:216–223.
6 Radic J, Ljutic D, Radic M, Kovacic V, Sain M, Dogig Curkovic K: The possible impact of dialysis modality on cognitive function in chronic dialysis patients. Neth J Med 2010;68: 153–157.
7 Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA: Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc Nephrol 2013;24: 353–363.
8 Jesus PA, Vieira-de-Melo RM, Reis FJ, Viana LC, Lacerda A, Dias JS, et al: Cognitive dysfunction in congestive heart failure: transcranial Doppler evidence of microembolic etiology. Arq Neuropsiquiatr 2006;64:207–210.
9 Drew DA, Bhadelia R, Tighiouart H, et al: Anatomic brain disease in hemodialysis patients: a cross-sectional study. Am J Kidney Dis 2013;61:271–278.
10 Weiner DE, Seliger SL: Cognitive and physical function in chronic kidney disease. Curr Opin Nephrol Hypertens 2014;3:291–297.
11 Skinner H, Mackaness C, Bedforth N, Mahajan R: Cerebral haemodynamics in patients with chronic renal failure: effects of haemodialysis. Br J Anaesth 2005;94:203–205.
12 Stefanidis I, Bach R, Mertens PR, Liakopoulos V, Liapi G, Mann H, et al: Influence of hemodialysis on the mean blood flow velocity in the middle cerebral artery. Clin Nephrol 2005;64: 129–137.
13 Ivey FM, Ryan AS, Hafer-Macko CE, Macko RF: Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. Stroke 2011;42:1994–2000.
14 Koufaki P, Greenwood S, Painter P, Mercer T: The BASES expert statement on exercise therapy for people with chronic kidney disease. J Sports Sci 2015;25:1–6.

15 Greenwood SA, Koufaki P, Mercer TH, MacLaughlin HL, Rush R, Lindup H, O'Connor E, Jones C, Hendry BM, Macdougall IC, Cairns HS: Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: a pilot randomized controlled trial. Am J Kidney Dis 2015;65:425–434.
16 Johansen KL, Painter P: Exercise in individuals with CKD. Am J Kidney Dis 2012;59:126–134.
17 Barber SE, Clegg AP, Young JB: Is there a role for physical activity in preventing cognitive decline in people with mild cognitive impairment? Age Ageing 2012;41:5–8.
18 Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, et al: Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. J Physiol 2008;586.16:4005–4010.
19 Endres M, Gertz K, Lindauer U, Katchanov J, Schultze J, Schrock H, et al: Mechanisms of stroke protection by physical activity. Ann Neurol 2003;54:582–590.
20 Gertz K, Priller J, Kronenberg G, Fink KB, Winter B, Schrock H, et al: Physical activity improves long-term stroke outcome via endothelial nitric oxide synthase-dependent augmentation of neovascularization and cerebral blood flow. Circ Res 2006;99:1132–1140.
21 Smart NA, Williams AD, Levinger I, Selig S, Howden E, Coombes JS, Fassett RG: Exercise & Sports Science Australia (ESSA) position statement on exercise and chronic kidney disease. J Sci Med Sport 2013;16:406–411.
22 Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al: Questionário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Rev Bras Ativ Fís Saúde 2001;6.
23 Pardini R, Matsudo S, Araújo T, Matsudo V, et al: Validação do questionário internacional de nível de atividade física (IPAQ – versão 6): estudo piloto em adultos jovens brasileiros. Rev Bras Cien e Mov 2001;9:45–51.
24 Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiat Res 1975;12:189–198.
25 Bertolucci PH, Brucki SM, Campacci SR, Juliano Y: [The Mini-Mental State Examination in a general population: impact of educational status] . Arq Neuropsiquiatr 1994; 52:1–7.
26 Brucki SM, Nitrini R, Caramelli P, Bertolucci PH, Okamoto IH: [Suggestions for utilization of the mini-mental state examination in Brazil]. Arq Neuropsiquiatr 2003;61:777–781.
27 Fujisaki K, Kanai H, Hirakata H, Nakamura S, Koga Y, Hattori F, et al: Midodrine hydrochloride and L-threo-3,4-dihydroxy-phenylserine preserve cerebral blood flow in hemodialysis patients with orthostatic hypotension. Ther Apher Dial 2007;11:49–55.
28 Ventura C: Ultrassonografia vascular: correlação com angiotomografia (ed): Giovanni Guido Cerri. Rio de Janeiro, Revinter, 2012.
29 Meneghelo RS, Araújo CGS, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM et al: III Diretrizes da Sociedade Brasileira de Cardiologia sobre Teste Ergométrico. Arq Bras Cardiol 2010;95(suppl 1):1–26.
30 Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L: Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment (Review). Cochrane Library 2008;3.
31 Paillard T: Preventive effects of regular physical exercise against cognitive decline and the risk of dementia with age advancement. Sports Med Open 2015;1:20.
32 Van Gelder BM, Tijhuis MA, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D: Physical activity in relation to cognitive decline in elderly men: the FINE Study. Neurology 2004; 63:2316–2321.
33 Schuit AJ, Feskens EJ, Launer LJ, Kromhout D: Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. Med Sci Sports Exerc 2001;33:772–777.
34 Guimarães FC, Amorim PR, Reis FF, Bonoto RT, Oliveira WC, Moura TA, et al: Pysical activity and better medication compliance improve mini-mental state examination scores in the elderly. Dement Geriatr Cogn Disord 2015;39:25–31.
35 Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M: Exercise level and cognitive decline: the MoVIES project. Alzheimer Dis Assoc Disord 2004;18:57–64.
36 Phillips C, Baktir MA, Srivatsan M, Salehi A: Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. Front Cell Neurosci 2014;8:170.
37 Vuori IM, Lavie CJ, Blair SN: Physical activity promotion in the health care system. Mayo Clin Proc 2013;88:1446–1461.
38 Schmidt W, Endres M, Dimeo F, Jungehulsing GJ: Train the vessel, gain the brain: physical activity and vessel function and the impact on stroke prevention and outcome in cerebrovascular disease. Cerebrovasc Dis 2013;35: 303–312.
39 Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE, et al: Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience 2003;117:1037–1046.
40 Rivera-Brown AM, Frontera WR: Principles of exercise physiology: responses to acute exercise and long-term adaptations to training. PM R 2012;4:797–804.
41 Gligoroska JP, Manchevska S: The effect of physical activity on cognition – physiological mechanisms. Mater Sociomed 2012;24:198–202.
42 Archer T: Physical exercise alleviates debilities of normal aging and Alzheimer's disease. Acta Neurol Scand 2011;123:221–238.
43 Lombroso P: Learning and memory. Rev Bras Pisquiatr 2004;26:207–210.
44 Burdette JH, Laurienti PJ, Espeland MA, Morgan A, Telesford Q, Vechlekar CD, et al: Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci 2010;2:23.
45 Colcombe S, Kramer AF: Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14:125–130.
46 Murrell CJ, Cotter JD, Thomas KN, Lucas SJ, Williams MJ, Ainslie PN: Cerebral blood flow and cerebrovascular reactivity at rest and during sub-maximal exercise: effect of age and 12-week exercise training. Age 2013;35:905–920.
47 Vicente-Campos D, Mora J, Castro-Piñero J, González-Montesinos JL, Conde-Caveda J, Chicharro JL: Impact of a physical activity program on cerebral vasoreactivity in sedentary elderly people. J Sports Med Phys Fitness 2012;52:537–544.
48 Bazan R, Braga GP, Luvizutto GJ, Hueb JC, Hokama NK, Zanati Bazan SG, et al: Evaluation of the temporal acoustic window for transcranial doppler in a multi-ethnic population in Brazil. Ultrasound Med Biol 2015;41: 2131–2134.