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Featured Article

Design of the ExCersion-VCI study: The effect of aerobic exercise on cerebral perfusion in patients with vascular cognitive impairment

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Abstract

There is evidence for a beneficial effect of aerobic exercise on cognition, but underlying mechanisms are unclear. In this study, we test the hypothesis that aerobic exercise increases cerebral blood flow (CBF) in patients with vascular cognitive impairment (VCI). This study is a multicenter single-blind randomized controlled trial among 80 patients with VCI. Most important inclusion criteria are a diagnosis of VCI with Mini-Mental State Examination $\geq$22 and Clinical Dementia Rating $\leq$0.5. Participants are randomized into an aerobic exercise group or a control group. The aerobic exercise program aims to improve cardiorespiratory fitness and takes 14 weeks, with a frequency of three times a week. Participants are provided with a bicycle ergometer at home. The control group receives two information meetings. Primary outcome measure is change in CBF. We expect this study to provide insight into the potential mechanism by which aerobic exercise improves hemodynamic status.

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1. Introduction

1.1. Background

For more than the last 40 years, the relationship between physical activity and cognitive functioning has been studied extensively in observational studies. These studies show a positive relationship between physical activity and cognitive functioning in healthy elderly individuals [1,2]. A physically active lifestyle in early and midlife seems to protect against cognitive decline later in late life [3,4]. However, a recent study failed to detect improvements in cognitive functioning in sedentary healthy elderly individuals after a physical activity program [5]. The methodology in that study was criticized for short exercise sessions with low dose intensity and being unsupervised [6]. Randomized controlled trials (RCTs) showed that aerobic exercise improves cognitive functioning, particularly executive functioning, in healthy elderly individuals [7,8]. Aerobic exercise in healthy elderly individuals was associated with larger brain volume in gray matter (GM) regions, in particular the anterior hippocampus and white matter (WM) regions [9,10]. However, RCTs of aerobic exercise in patients with cognitive impairment and dementia are limited and show mixed results, which may be partly because of methodological issues [11,12].

The biological mechanisms underlying the apparent positive effects of physical activity on cognitive functioning are still poorly understood. Reviews that summarize the findings of studies investigating the relationship between physical activity and cognition stress the need to perform RCTs with measures of underlying mechanisms as primary outcome measure [11,13]. Understanding the mechanism is essential before implementing physical activity as preventive therapy [13,14].

Earlier studies have tried to explain the beneficial effect of physical activity on cognition. Some theories of the potential mechanism include reduction of inflammation, increase in growth factors and neurotransmitters, and neurogenesis in addition to reduction in chronic (cardiovascular) diseases and improvement in vascular health [13]. Mouse models have demonstrated a beneficial effect of aerobic exercise on stroke prevention [13,15,16]. Furthermore, studies with rats suggest that the effect of aerobic exercise on cognitive functioning may act through an increased perfusion of the brain [17]. The results of an early observational study in healthy elderly individuals support the relationship among physical activity, cerebral blood flow (CBF), and cognition [18]. In this latter study, retirees who were physically inactive showed significant declines in CBF for more than 4 years and also performed worse on cognitive tests at the end of the study in comparison with retirees who were physically active. This suggests that the link between physical activity and cognition may be mediated, at least in part, by an improvement in CBF.

Vascular cognitive impairment (VCI) is one of the most important causes of cognitive impairment and dementia [19]. VCI is defined as cognitive impairment associated with and thought to be because of cerebrovascular disease. In addition to cognitive decline, patients with VCI frequently suffer from behavioral and psychological symptoms. As a consequence, VCI has a tremendously negative impact on daily functioning and quality of life for patients and their families. Cognitive impairment in VCI may be partly mediated by progressive cerebrovascular damage resulting in a decline in CBF [20]. Treatments that could improve cerebral hemodynamics may also improve cognitive functioning in patients with VCI [21,22]. However, currently secondary prevention by modifying vascular risk factors and, if indicated, prescribing antithrombotic agents is the only available evidence-based treatment for patients with VCI. Despite the increasing prevalence of cerebrovascular disease, few intervention studies focus on this specific group of patients. Aerobic exercise may be a promising approach to delay, minimize, or even prevent the progression of VCI [23,24].

Here, we describe the design of exercise on cerebral perfusion in patients with vascular cognitive impairment (ExCersion-VCI), which aims to study the effect of an aerobic exercise program of 14 weeks on CBF in 80 patients with VCI, in a proof-of-concept single-blind RCT.

Our *primary objective* is to assess whether aerobic exercise leads to increased CBF in patients with VCI, determined by arterial spin labeling magnetic resonance imaging (ASL-MRI). Our *secondary objectives* are to assess the effect of aerobic exercise on (1) cognitive and physical functioning, (2) blood biomarkers, (3) brain function and structure, and (4) (instrumental) activities of daily living and quality of life. In a separate add-on study, we assess the effect of aerobic exercise on cerebral autoregulation efficacy (CA) and cerebral vasomotor reactivity (CVMR) as major physiological pathways involved in controlling CBF.

2. Methods

The ExCersion-VCI is a multicenter single-blind RCT. ExCersion-VCI is part of the Heart-Brain Connection, a national multidisciplinary collaborative network of six Dutch university medical centers, funded by CardioVasculair Onderzoek Nederland [25]. The medial ethics committee/institutional review board of the VU University Medical Center (VUmc) in Amsterdam approved the study. Dutch Trial Register: NTR5668 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5668).

2.1. Participants

Participants are patients with VCI without dementia. We include 80 participants who meet the inclusion and exclusion criteria as given in Table 1.

2.2. Procedures

Participants undergo screening, baseline and postassessment (Fig. 1 and Table 2).

Eligible patients are recruited through the outpatient memory clinic of the VUmc and treating physicians in the University Medical Center Utrecht (UMCU). Patients eligible for participation are provided with study information and are given at least a week for consideration. When interested in participation, the participant provides written informed consent before performance of any study-related procedure. The aim of the screening visit is to assess possible safety concerns before measuring physical fitness. This visit includes the Physical Activity Readiness Questionnaire, a screening tool for readiness to perform exercise [26]. When study participation is considered safe, the baseline assessment is scheduled. Baseline and postassessment are performed with a maximum of 14 days before the first and 14 days after the last exercise session. We aim to schedule all assessments in one day, and we attempt to schedule baseline and postassessments on the same time of the day to limit diurnal influences on outcome parameters.

2.3. Randomization and blinding

After baseline assessment, participants are allocated to either the aerobic exercise program or to the control group using the so-called minimization approach, to ensure balance between the intervention and control group [27]. Minimization is a method of adaptive stratified sampling; patients are sequentially assigned by attempting to minimize the total imbalance between both groups using prognostic factors [28]. Minimization is performed using the Minim software with a 1:1 allocation ratio and equal weighting for four minimization factors: disease severity (Clinical Dementia Rating 0 vs. 0.5), age (<65 vs. >65 years), gender, and center [29]. An independent researcher blinded for participants' identity performs the randomization. Outcome assessors are blinded for group allocation, but it is not possible to blind participants and personnel supervising the interventions. Before postassessment, participants are instructed not to disclose their group allocation to the outcome assessor.

3. Intervention

Participants are randomized to either the aerobic exercise group or to the control group.

3.1. Aerobic exercise group

The aerobic exercise program is designed to improve cardiorespiratory fitness. Participants are provided with a bicycle ergometer (Kettler Ergometer E7, Ense, Deutschland) at home to perform exercise sessions. The total exercise program lasts 14 weeks with a frequency of three times per week. In total, there are 42 exercise sessions; each session consists of warming up (10 minutes), core activity (25 minutes), and cooling down (10 minutes). The core activity is interval training, based on the 4 × 4 minutes aerobic interval training model (Fig. 2). This type of training has been used in several studies with healthy subjects and various cardiac patients [30]. The interval training contains four cycles of different exercise intensities. Each cycle lasts 7 minutes: 4 minutes of high intensity exercise (85%–95% heart rate peak [HR_{peak}]), followed by 3 minutes of low-to-moderate intensity exercise (60%–70% HR_{peak}). The intensity of each cycle is individualized for participants using their individual activity level (HR_{peak}), assessed during a maximal cardiopulmonary exercise test. The HR is

Table 1
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥50 years • Cognitive complaints • Clinical Dementia Rating score ≤0.5 and Mini-Mental State Examination ≥22 • Presence of a primary caregiver • On brain MR, moderate-to-severe white matter lesions (Fazekas scale > 1) and/or (lacunar) infarct(s) and/or intracerebral (micro-) hemorrhage(s) *OR* On brain MR, mild white matter lesions (Fazekas scale = 1) and at least two of the following vascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, or clinically manifest vascular disease (last event > 6 mo ago), clinically manifest vascular disease comprises peripheral arterial disease, myocardial infarction, percutaneous coronary intervention/coronary artery bypass graft, and/or stroke	• Diagnosis of dementia • Contraindication for MRI or unable to undergo MRI protocol because of a physical condition • Participation in aerobic exercise program (moderate-to-hard intensity) ≥ twice weekly on a regular basis • Major neurologic, psychiatric, cardiac, musculoskeletal, or other medical disease that affects cognition and/or mobility and constitutes a contraindication to perform aerobic exercise training • Participation in another clinical trial

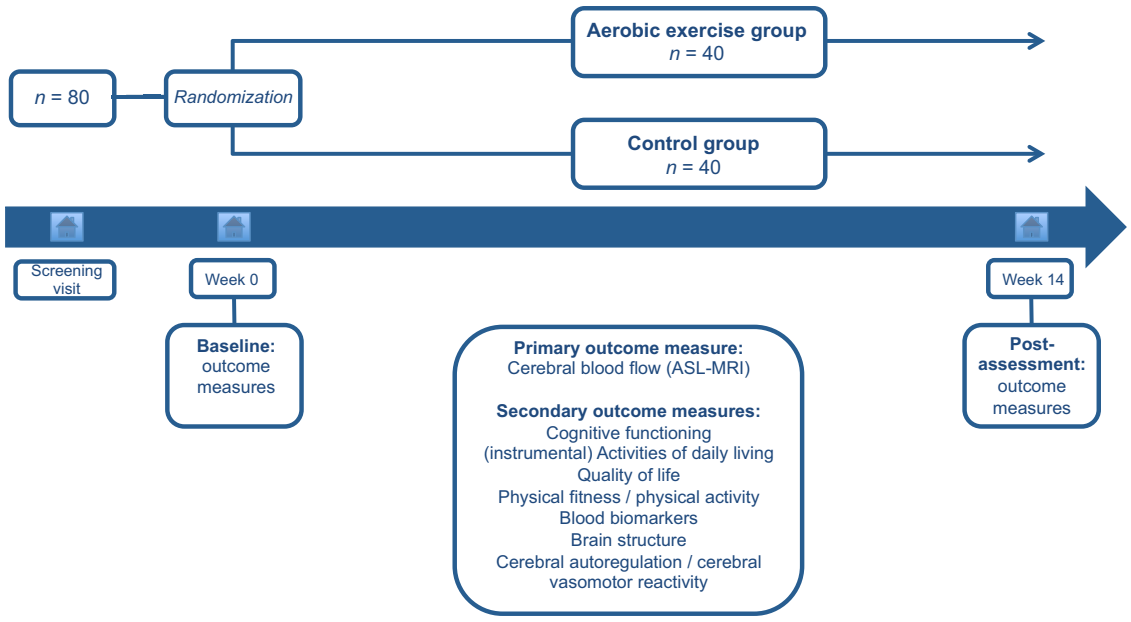

Fig. 1. Schematic overview of study design.

Table 2
Overview of assessments per visit

Measurement	Screening	Baseline	Postassessment
Demographic characteristics	X		
MMSE	X		X
Medical history	X		
Vascular risk factors	X		
PAR-Q	X		
Weight and height	X		X
Waist and hip circumference	X		X
12-Lead ECG	X		X
Transthoracic echocardiography*		X	
Blood pressure	X	X	X
Neuropsychological assessment		X	X
Brain MRI		X	X
Cardiac MRI		X	
Physical fitness (6MWT, VO_{2max})		X	X
Physical activity (activity monitor)	X		X
Blood samples		X	X
General functioning (DAD, CDR, iADL)		X	X
Neuropsychiatric measures		X	X
Quality of life		X	X
Hemodynamic parameters†		X	X
Cerebral parameters†		X	X
Respiratory parameters†		X	X

Abbreviations: CDR, Clinical Dementia Rating; DAD, disability assessment of dementia; ECG, electrocardiography; iADL, instrumental activities in daily life; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; 6MWT, six-minute walk test; PAR-Q, Physical Activity Readiness Questionnaire; VO_{2max}, maximum oxygen consumption.

*Transthoracic echocardiography is only performed in Amsterdam.

†These parameters are part of the add-on study.

monitored using an HR monitor to ensure that the participant exercises with the intended intensity.

A buddy, a physical therapist in training, supervises 13 of the 42 sessions. Primary goals of the buddy are to keep participants motivated for adherence to the program and to assure safety of the program. Supervised sessions are frequent in the beginning of the intervention period and become less frequent during the course of the program. On the first day of the exercise program, the buddy informs the participant about the program (e.g., importance of warming up and cooling down, instructions about safe exercising [prevention of injuries and use of appropriate clothing]). The provided bicycle ergometer records training sessions to control adherence. Also, information on adherence is recorded by the participant and buddy using a diary. Participants monitor the intensity of each session using the Borg Rating of Perceived Exertion [31] to rate the amount of effort. Furthermore, participants record their ordinary daily physical activities.

3.2. Control group

Participants in the control group receive two individual information sessions of 45 minutes in a period of 14 weeks. The information sessions cover information about VCI and cardiovascular risk factors. To control for the level of physical activity, participants in the control group are asked to record their physical activities in a diary. In addition, the control group receives usual care, which comprises planned outpatient visits (usually every 6 months, so one or none within the study period).

To strengthen recruitment and adherence to the program, participants in the control group are provided with a bicycle

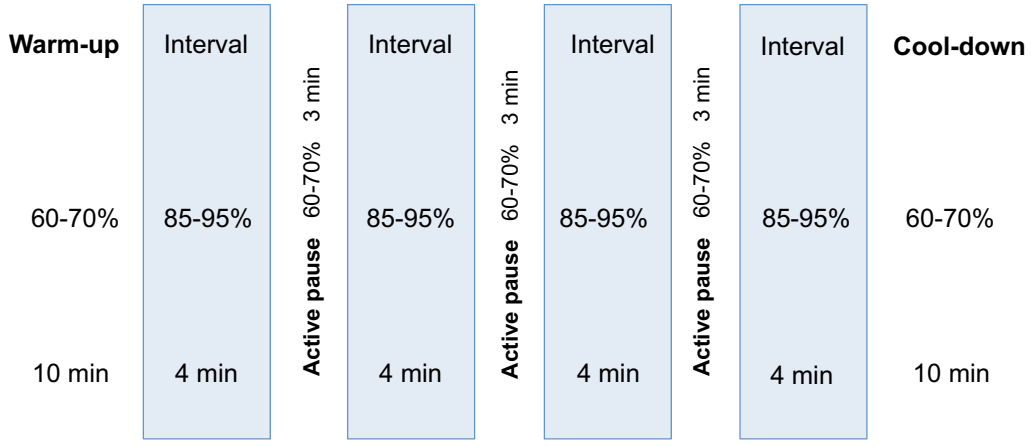

Fig. 2. 4 × 4 minutes aerobic interval training model.

ergometer at home for 14 weeks *after* postassessment as an introduction to aerobic exercise and encouragement to participate in sport activities.

4. Measures

4.1. Primary outcome measure

CBF is measured with ASL-MRI, a quantitative and noninvasive technique to measure CBF by using magnetically labeled arterial blood protons as endogenous tracer. The MRI protocol consists of two ASL-sequences: (1) perfusion imaging (pseudocontinuous ASL [pCASL]) to quantify CBF, and (2) multiphase pCASL with multiple postlabel delay acquisitions to measure arterial transit time. Transit time is the duration for the magnetically labeled arterial blood water to travel from the labeling region in the neck region to the tissue of interest. Transit time varies across the brain and is dependent on the arterial size, stiffness, and the cardiac output fraction [32,33]. The influence of transit time is of particular interest in patients with altered hemodynamic status, for example, in patients with VCI. Moreover, the estimation of transit time aids in improving CBF quantification by means of pCASL. Furthermore, to correct for possible confounders on ASL-MRI, participants are instructed to refrain from alcohol during 24 hours before the MRI, from caffeine and smoking during the preceding 6 hours, and from eating 1 hour before the MRI measurements.

4.2. Secondary outcome measures

4.2.1. Cognitive functioning, (instrumental) activities of daily living, and quality of life

In this project, we use the standardized comprehensive test battery that has been developed in context of the Dutch Parelsnoer Initiative [34] and is designed to cover global cognitive

Table 3
Standardized neuropsychological assessment and measures of daily functioning neuropsychiatry and quality of life [35]

Test/questionnaire	Domain(s)
Cognitive functioning	
Mini-Mental State Examination	Global cognition
15-Word-Auditory Verbal Learning Test (AVLT)*	Episodic memory
Visual Association Test, short version	Implicit associative visual learning
Digit-Span of the WAIS-III (forward and backward)	Working memory
Fluency, 60 s (animals)	Verbal word fluency/semantic memory
Letter Digit Substitution Test, 90 s	Information processing speed
Stroop Color Word Test	Information processing speed, attention, and response inhibition/executive functioning
Trail Making Test (part A and B)	Information processing speed, attention, and concept shifting/executive functioning
Daily functioning, neuropsychiatry, and quality of life	
Clinical Dementia Rating	Global rating of dementia severity
Amsterdam instrumental activities in daily life	Activities of daily life
Disability Assessment of Dementia	Activities of daily life
15-item Geriatric Depression Scale	Depressive symptoms
Starkstein Apathy Scale [36]	Apathy symptoms
EuroQol-5D, including EuroQol Visual Analog Scale [37]	Health-related quality of life
Short Stroke-Specific Quality of Life Scale [38]	Quality of life in patients with stroke

*To minimize test and retest effect, a parallel version of the 15-Word-AVLT is administered at the postassessment.

function and four major cognitive domains including memory, attention, language, and executive functioning (Table 3). Furthermore, we assess general functioning and instrumental activities of daily living necessary to establish a diagnosis of dementia. We use validated scales of depressive symptoms, apathy, and quality of life.

4.2.2. Physical fitness and physical activity

Cardiorespiratory fitness is assessed by a maximum capacity test (maximal oxygen consumption [VO_{2max} test]) on an electromagnetic bicycle ergometer. Work rate is progressively increased with 10, 15, 20, or 25 W per minute during an individualized cycle ergometer ramp protocol. The protocol is based on the estimated physical capacity of the participants (i.e., for deconditioned individuals an increment of 10 W per minute, for conditioned individuals 20 W per minute). Stopping criteria for the VO_{2max} test, as recommended by the American College of Sports Medicine, were physical exhaustion, rounds per minute <60, or safety reasons [39]. HR recordings (12-lead electrocardiogram) and gas exchange measurements (breath-by-breath gas analysis; Quark CPET, COSMED SRl, Rome, Italy) are recorded throughout the test, and blood pressure is measured every 3 minutes. In addition, participants perform a 6-minute walk test (6MWT) [40]. Both after the VO_{2max} test as after the 6MWT, participants are asked to monitor the intensity using Borg's Rating of Perceived Exertion. Amount, frequency, and intensity of physical activity in daily life are monitored by a triaxial activity monitor (ActiGraph GT3X+, ActiGraph, Pensacola, FL), which is worn for seven consecutive days after screening and postassessment. The Physical Activity Scale in the Elderly is used to estimate the participants' physical activity in daily life [41]. This self-report questionnaire is a valid measure of physical activity in older individuals.

4.2.3. Blood biomarkers

We investigate both systemic and organ-specific biomarkers in blood that relate to functional or structural abnormalities in one or more of the components of the heart-brain axis and might be influenced by the intervention. For the systemic biomarkers, we focus on biomarkers linked to processes that are involved in heart failure, atherosclerosis, and VCI, in particular, abnormalities in lipid metabolism, insulin resistance/dysglycemia (i.e., glucose, insulin, and HbA1c), and inflammation (i.e., plasma C-reactive protein, fibrinogen, interleukin (IL)-1, IL-6, IL-10, soluble growth stimulation expressed gene 2 (s-ST2), and tumor necrosis factor α) and anemia (i.e., hemoglobin). For organ-specific biomarkers (i.e., markers that reflect pathogenic processes in organ-specific components of the heart-blood vessels-brain axis), we assess markers of heart failure and cardiac fibrosis (i.e., serum NT-proBNP, high-sensitivity TnT, galectin-3, and serum creatinine) and remodeling of blood vessel pathology (i.e., plasma homocysteine and endostatin) and of Alzheimer-type pathology (i.e., plasma Aβ40 and Aβ42). Finally, we consider biomarkers that are specifically involved in potential other mechanisms of the effect of the intervention on cognition (i.e., brain-derived neurotrophic factor, insulin-like growth factor 1 and vascular endothelial growth factor, and thyroid-stimulating hormone) [42]. Blood samples were collected in a nonfasting state. Participants are requested to provide informed consent for DNA storage for genetic analyses within the scope of the current research project (i.e., apolipoprotein E polymorphism [*APOE*] genotype) and currently unknown genetic variants that might be involved in risk of cardiovascular disease and/or cognitive decline.

4.2.4. Brain structure

Brain and cardiac (see subsequently) MRI is acquired on a Philips Gemini 3 T PET-MR scanner in the VUmc and a Philips Ingenia 3 T scanner in the UMCU (Philips Healthcare Europe, Best, the Netherlands). Scans are screened by local radiologists for the occurrence of clinically relevant findings; visual ratings will be applied to characterize cerebrovascular involvement. The brain protocol includes, besides two ASL sequences (see primary outcome measure), T1-weighted, fluid attenuated inversion recovery, and susceptibility weighted imaging images. The quantitative imaging biomarkers from the brain MRI are computed with existing software and software that is specifically designed for the Heart-Brain Connection and for ExCersion-VCI. Brain MRIs are processed with two automated pipelines resulting in the following biomarkers: (1) volumes in milliliters (mL) of total brain GM, WM, cerebrospinal fluid, and white matter hyperintensities, and (2) total brain volume, GM volume, and WM volume of 83 structural brain regions (mL; obtained using atlas-based segmentation with Hammer's atlas).

4.2.5. Cerebral autoregulation and cerebral vasomotor reactivity (add-on study)

All participants are invited to participate in an add-on study. We assess dynamic CA and CVMR at baseline and postassessment. Dynamic CA is quantified in the frequency domain as the counter-regulatory capacity to maintain CBF velocity (CBFv; transcranial Doppler ultrasonography) during spontaneous oscillations in blood pressure (finger plethysmography) [43]. Both CBFv and blood pressure are continuously measured in the supine and standing position of the participant.

CVMR is quantified by noninvasive and continuous measurements of CBFv and end-tidal CO_2 (using a nasal cannula) during hyperventilation, normal breathing, and normal breathing when inhaling a gas mixture containing 5% CO_2 and 95% O_2 (i.e., carbogen). We perform an additional bicycle test to quantify the increase in CBFv in response to sympathetic stimulation. The work rate is progressively increased in a similar manner as during the protocol that measures VO_{2max}, until 70% of maximal HR has been reached.

4.3. Demographic and other baseline variables

4.3.1. Clinical data

Data on risk factors for VCI and relevant comorbidities are collected according to the framework of the recent American Heart Association position statement on VCI [44]. Nonmodifiable risk factors include demographic factors (gender, age, and ethnicity). Modifiable risk factors include lifestyle factors (education, physical activity, alcohol use, and smoking), depression, current medication use, and cardiovascular risk factors (including blood pressure, body mass index and waist-hip ratio, markers of glucose, and lipid metabolism).

4.3.2. Cardiac MRI

Cardiac MRI is performed at baseline with electrocardiographic gating and a phased array cardiac receiver coil. Cine images in two-chamber left, two-chamber right, three-chamber, four-chamber, and short-axis views are obtained using a balanced steady-state free precession pulse sequence in breath-hold. Anatomy and dimensions of the thoracic aorta are visualized using a balanced steady-state free precession pulse sequence. Free breathing two-dimensional through-plane velocity-encoded flow imaging is performed to measure mitral inflow and ascending/descending aorta flow at the level of the pulmonary trunk. The following parameters are determined: dimensions and function of the atria and ventricles, left ventricular ejection fraction, cardiac output, left ventricular mass, diastolic dysfunction (*E*/*A* ratio mitral inflow), left atrial volume, valve abnormalities, and aortic pulse wave velocity.

4.3.3. Transthoracic echocardiography

All participants included in the VUmc undergo transthoracic ultrasound echocardiography. This assessment includes systolic and diastolic ventricular function both left and right sided, atrial and ventricular dimensions and valve function. Echocardiography is performed in standard parasternal, apical, and subcostal views and is noninvasive, harmless, and routinely used in cardiac patients.

5. Statistical methods

5.1. Sample size

The primary outcome measure is change in CBF after 14 weeks. To our knowledge, no former study has investigated the effect of aerobic exercise on CBF in patients with VCI. In a Cochrane review, evaluating 11 RCTs comparing aerobic exercise training with any other or no intervention in healthy participants older than 55 years, it was concluded that aerobic exercise training is beneficial for cognitive functioning [7]. A large effect size on cognitive functioning was found on attention (mean summary effect size of 0.50), a moderate effect size was observed for cognitive speed (mean summary effect size of 0.26). Studies in this review used the same neuropsychological tests as in the present study. In this study, we focus on the underlying mechanism of aerobic exercise on cognitive functioning. Assuming that aerobic exercise exerts its effect on cognition through an improved CBF, we suspect that the effect size on CBF is larger. On the basis of the studies focusing on CBF in patients with dementia [45,46], we assume a large effect size of 0.60. This corresponds to a difference in (mean change in CBF of 3 $\pm$ 5 mL/100 mg/min), as was found in a longitudinal study of patients with hypertension, compared with patients without hypertension [46]. Preliminary calculations suggest that for an effect size of 0.6, a total number of 74 patients randomized 1:1 to the intervention and control group (N = 37 in each group) is needed to detect an effect of aerobic exercise on CBF with a significance level of 0.05 and statistical power of 80%. To correct for potential dropout, 40 patients are enrolled in each arm.

5.2. Data analysis

Statistical analyses of the outcome parameters are performed using intention-to-treat analyses. In addition, a per-protocol analysis is performed to investigate the biological effect of physical activity.

Analysis of variance for repeated measures is used to examine an effect of the intervention with intervention as between-groups-variable and time as within-groups-variable; age, sex, and measures of small vessel disease (white matter hyperintensities and lacunes) are entered as covariates. CBF is the dependent variable, in additional models the secondary outcome measures (i.e., cognition, structural MRI, physical fitness, blood biomarkers) are used as dependent variables.

Effect modification of cardiac output is examined using interaction terms between randomization group (intervention vs. control group) and cardiac output. The rationale for this analysis is that we expect higher cardiac output to affect the magnitude of response to aerobic exercise. Stratified analysis (high vs. low cardiac output) is performed when there is a significant interaction ($P < .10$). The significance level for the analyses of the outcome variables is set at $<.05$.

6. Discussion

ExCersion-VCI is part of the Heart-Brain Connection, a national interdisciplinary collaborative network [25]. In this consortium, we aim to give insight into the relationships between cardiovascular and hemodynamic factors and brain structure and cognitive functioning in VCI. The Heart-Brain Connection is a unique multidisciplinary collaboration including neurologists, cardiologists, neuropsychologists, radiologists, and MR-physicists.

This study is a proof-of-principle intervention study, which aims to investigate the effect of aerobic exercise on CBF in VCI patients. This study is a multicenter single-blind RCT. Patients are randomized in an aerobic exercise group or control group. Primary outcome measure is change in CBF as measured with ASL-MRI. Epidemiologic studies indicate exercise as a contributor to healthy brain aging with the potential to delay the onset of cognitive impairment and dementia. Nevertheless, questions about the intensity, duration, and frequency of exercise remain. For instance, we do not know what the most optimal and effective exercise program is for different patient groups. Although the prevalence of VCI and dementia increases, few RCTs of exercise have been conducted in populations at high-risk for dementia. Also, few RCTs have investigated primarily the potential mechanism behind the effect of aerobic exercise on cognitive functioning or investigated this mechanism in patients who are at risk for dementia. To emphasize the potential of exercise in preventing or delaying dementia, we need to understand the underlying mechanisms behind the effect of exercise on cognitive functioning. Earlier findings suggest that exercise sets into motion an improvement in brain structure and function because of modulation of vascular risk factors, increase in growth factors, stimulation of neurogenesis, angiogenesis, and enhancement of growth and protection of neurovasculature, which could lead to an improvement in CBF [16,47–49]. ExCersion-VCI is an important step in quantifying a possible improvement of CBF, which can lead to improved cognitive functioning in VCI patients. Aerobic exercise, if effective, represents an affordable and accessible method in halting and may be even preventing ongoing cognitive decline ultimately progressing to dementia in patients with VCI.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2017.02.002.

RESEARCH IN CONTEXT

1. Systematic review: We performed a literature search using PubMed regarding the mechanism behind the effect of aerobic exercise on cognition.
2. Interpretation: Exercise programs aiming at improvement of physical fitness have shown beneficial effects on cognition in healthy elderly individuals, but whether it will provide such effects in cognitively impaired patients is uncertain. Furthermore, aerobic exercise has been found to reduce the risk of stroke, suggesting that the beneficial effect of aerobic exercise on cognition is secondary to an increase in cerebral blood flow.
3. Future directions: In this study we hypothesize that aerobic exercise will have a positive effect on cerebral blood flow in patients with VCI. We expect exercise on cerebral perfusion in patients with VCI to provide further insight into the potential of aerobic exercise to improve hemodynamic status and hence improve cognitive functioning in patients with VCI.

References

[1] Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. J Neurol Neurosurg Psychiatry 2007;78:929–35.
[2] Rosano C, Simonsick EM, Harris TB, Kritchevsky SB, Brach J, Visser M, et al. Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. Neuroepidemiology 2005;24:8–14.
[3] Fratiglioni L, Paillard-borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004;3:343–53.
[4] Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302:627–37.
[5] Sink KM, Espeland MA, Castro CM, Church T, Cohen R, Dodson JA, et al. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults. JAMA 2015;314:781.
[6] Poulin MJ, Eskes GA, Hill MD. Physical activity vs health education for cognition in sedentary older adults. JAMA 2016;315:26–7.
[7] Angevaren M, Aufdemkampe G, Hjj V, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment (Review). Cochrane Database Syst Rev 2008;CD005381.
[8] Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14:125–30.
[9] Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, Mcauley E, et al. Brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006;61:1166–70.
[10] Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 2011;108:3017–22.

[11] Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med 2010;72:239–52.
[12] Groot C, Hooghiemstra AM, Raijmakers PG, van Berckel BN, Scheltens P, Scherder EJ, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing Res Rev 2016;25:13–23.
[13] Brown BM, Peiffer JJ, Martins RN. Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? Mol Psychiatry 2013;18:864–74.
[14] 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;35:303–12.
[15] Williams PT. Reduction in incident stroke risk with vigorous physical activity: evidence from 7.7-year follow-up of the national runners' health study. Stroke 2009;40:1921–3.
[16] Endres M, Gertz K, Lindauer U, Katchanov J, Nickenig G, Kuschinsky W, et al. Mechanisms of stroke protection by physical activity. Ann Neurol 2003;54:582–90.
[17] 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; 117:1037–46.
[18] Rogers RL, Meyer JS, Mortel KF. After reaching retirement age physical activity sustains cerebral perfusion and cognition. J Am Geriatr Soc 1990;38:123–8.
[19] Gorelick PB, Bowler JV. Advances in vascular cognitive impairment. Stroke 2010;41:e93–8.
[20] Marshall RS, Lazar RM. Pumps, aqueducts, and drought management: vascular physiology in vascular cognitive impairment. Stroke 2011; 42:221–6.
[21] Zuccalà G, Onder G, Marzetti E, Monaco MR, Cesari M, Cocchi A, et al. Use of angiotensin-converting enzyme inhibitors and variations in cognitive performance among patients with heart failure. Eur Heart J 2005;26:226–33.
[22] Sasoh M, Ogasawara K, Kuroda K, Okuguchi T, Terasaki K, Yamadate K, et al. Effects of EC-IC bypass surgery on cognitive impairment in patients with hemodynamic cerebral ischemia. Surg Neurol 2003;59:455–60.
[23] Middleton L, Kirkland S, Rockwood K. Prevention of CIND by physical activity: different impact on VCI-ND compared with MCI. J Neurol Sci 2008;269:80–4.
[24] Pedersen BK, Saltin B. Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports 2015;25:1–72.
[25] Van Buchem MA, Biessels GJ, Brunner La Rocca HP, De Craen AJ, Van Der Flier WM, Ikram MA, et al. The heart-brain connection: a multidisciplinary approach targeting a missing link in the pathophysiology of vascular cognitive impairment. J Alzheimers Dis 2014;42:S443–51.
[26] Thomas S, Reading J, Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Can J Sport Sci 1992;17:338–45.
[27] Scott NW, Hons MA, Sc M, Mcpherson GC, Hons BS, Ramsay CR, et al. The method of minimization for allocation to clinical trials: a review. Control Clin Trials 2002;23:662–74.
[28] Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31:103–15.
[29] Evans S, Day S, Royston P. MINIM: minimisation program for allocating patients to treatments in clinical trials. Londen: Department of Clinical Epidemiology, the London Medical College; 1995.
[30] Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation. Eur J Prev Cardiol 2013;20:442–67.
[31] Borg G. Ratings of perceived exertion and heart rates during short-term cycle exercise and their use in a new cycling strength test. Int J Sports Med 1982;03:153–8.
[32] Lee GR, Hernandez-garcia L, Noll DC. Functional imaging with Turbo-CASL: transit time and multislice imaging considerations. Magn Reson Med 2007;669:661–9.
[33] Campbell AM, Beaulieu C. Pulsed arterial spin labeling parameter optimization for an elderly population. J Magn Reson Imaging 2006; 23:398–403.
[34] Aalten P, Ramakers IH, Biessels GJ, de Deyn PP, Koek HL, Olderikkert MG, et al. The Dutch Parelsnoer Institute—neurodegenerative diseases; methods, design and baseline results. BMC Neurol 2014;254:1–8.
[35] van der Flier WM, Pijnenburg YA, Prins N, Lemstra AW, Bouwman FH, Teunissen CE, et al. Optimizing patient care and research: the Amsterdam dementia cohort. J Alzheimers Dis 2014; 41:313–27.
[36] Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992;4:134–9.
[37] The EuroQol Group. EuroQol*—a new facility for the measurement of health-related quality of life. Health Policy (New York) 1990; 16:199–206.
[38] Post M, Boosman H, van Zandvoort M, Passier P, Rinkel G, Visser-Meily J. Development and validation of a short version of the Stroke-Specific Quality of Life Scale. J Neurol Neurosurg Psychiatry 2010;3:1–14.
[39] Pescatello LS, Medicine AC of S. ACSM's guidelines for exercise testing and prescription. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
[40] Enright PL. The six-minute walk test. Respir Care 2003;48:783–5.
[41] Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46:153–62.
[42] Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 2007;30:464–72.
[43] Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. Am J Physiol 1998;274:233–41.
[44] Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42:2672–713.
[45] Binnewijzend MA, Kuijer JP, Benedictus MR, van der Flier WM, Wink AM, Wattjes MP, et al. Cerebral blood flow measured arterial spin-labeling MR imaging in Alzheimer disease and mild cognitive impairment. Radiology 2013;267:221–30.
[46] Muller M, van der Graaf Y, Visseren FL, Mali WP, Geerlings MI. Hypertension and longitudinal changes in cerebral blood flow: the SMART-MR study. Ann Neurol 2012;71:825–33.
[47] Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol 2009; 94:1062–9.
[48] Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 2010;67:71–9.
[49] Ding YH, Li J, Zhou Y, Rafols JA, Clark JC, Ding Y. Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. Curr Neurovasc Res 2006;3:15–23.