Chapter 3

DESIGN OF THE EXCERSION-VCI STUDY: THE EFFECT OF AEROBIC EXERCISE ON CEREBRAL PERFUSION IN PATIENTS WITH VASCULAR COGNITIVE IMPAIRMENT


ABSTRACT

Background: 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 leads to increased cerebral blood flow (CBF) in patients with vascular cognitive impairment (VCI).

Methods: ExCersion-VCI is a multi-center, single-blind randomized controlled trial among 80 patients with VCI. Most important inclusion criteria are a diagnosis of VCI with MMSE≥22 and CDR≤0.5. Participants are randomized into an aerobic exercise program group or a control group. The aerobic exercise program aims to improve cardiorespiratory fitness and takes 14 weeks, with a frequency of 3 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 in rest, measured with Arterial Spin Labeling-MRI.

Discussion: We expect ExCersion-VCI to provide insight in the potential mechanism by which aerobic exercise improves hemodynamic status.
INTRODUCTION

Background
Over 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. A physically active lifestyle in early and midlife seems to protect against cognitive decline later in life. However, a recent study failed to detect improvements in cognitive functioning in sedentary healthy elderly after a physical activity program. The methodology in that study was criticized for short exercise sessions with low dose intensity and being unsupervised. Randomized controlled trials (RCTs) showed that aerobic exercise improves cognitive functioning, particularly executive functioning, in healthy elderly. Aerobic exercise in healthy elderly was associated with larger brain volume in grey matter regions, in particular the anterior hippocampus, and white matter regions. However, RCTs of aerobic exercise in patients with cognitive impairment and dementia are limited and show mixed results, which may be partly due to methodological issues.

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. Understanding the mechanism is essential before implementing physical activity as preventive therapy.

Earlier studies have tried to explain the beneficial effect of physical activity on cognition. Some theories of 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. Mouse models have demonstrated a beneficial effect of aerobic exercise on stroke prevention. Furthermore, studies with rats suggest that the effect of aerobic exercise on cognitive functioning may act through an increased perfusion of the brain. The results of an early observational study in healthy elderly supports the relationship between physical activity, CBF and cognition. In this latter study, retirees who were physically inactive showed significant declines in CBF over 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. VCI is defined as cognitive impairment associated with and thought to be due to cerebrovascular disease. In addition to cognitive decline,
patients with VCI frequently suffer from behavioural and psychological symptoms. As 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.\textsuperscript{20} Treatments that could improve cerebral hemodynamics may also improve cognitive functioning in patients with VCI.\textsuperscript{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.\textsuperscript{23,24}

Here we describe the design of 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 \textbf{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 \textbf{secondary objectives} are to assess the effect of aerobic exercise on 1) cognitive and physical functioning, 2) blood biomarkers, 3) brain function and structure, 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 autoregulatory efficacy (CA) and cerebral vasomotor reactivity (CVMR) as major physiological pathways involved in controlling CBF.

\section*{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 (CVON).\textsuperscript{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).

\textbf{Participants}

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

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>· Age: ≥50 years</td>
<td>· Diagnosis of dementia</td>
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<tr>
<td>· Cognitive complaints</td>
<td>· Contra-indication for MRI or unable to undergo MRI protocol due to a physical condition</td>
</tr>
<tr>
<td>· Clinical Dementia Rating (CDR) score ≤ 0.5 and MMSE ≥ 22</td>
<td>· Participation in aerobic exercise program (moderate-to-hard intensity) ≥ twice weekly on a regular basis</td>
</tr>
<tr>
<td>· Presence of a primary caregiver</td>
<td>· Major neurological, psychiatric, cardiac, musculoskeletal or other medical disease that affects cognition and/or mobility and constitutes a contra-indication to perform aerobic exercise training</td>
</tr>
<tr>
<td>· On brain MR, moderate to severe white matter lesions (Fazekas &gt; 1) and/or (lacunar) infarct(s) and/or intracerebral (micro-)haemorrhage(s) OR On brain MR, mild white matter lesions (Fazekas = 1) and at least two of the following vascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking or clinically manifest vascular disease (last event &gt; 6 months ago), clinically manifest vascular disease comprises peripheral arterial disease, myocardial infarction, percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG), and/or stroke</td>
<td>· Participation in another clinical trial</td>
</tr>
</tbody>
</table>

### Procedures

Participants undergo screening, baseline and post-assessment (Figure 1 and Table 2). Eligible patients are recruited through the outpatient memory clinic of VUmc and treating physicians in 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 prior to 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 (PAR-Q), a screening tool for readiness to perform exercise. When study participation is considered safe, the baseline assessment is scheduled. Baseline- and post-assessment 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 post-assessments on the same time of the day to limit diurnal influences on outcome parameters.
Figure 1. Schematic overview of study design.

Randomisation and blinding
Following 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. 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. Minimization is performed using the Minim software with a 1:1 allocation ratio and equal weighting for four minimization factors: disease severity (CDR=0 vs. CDR=0.5), age (age<65 years vs. age>65 years), gender and center. 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. Prior to post-assessment, participants are instructed not to disclose their group allocation to the outcome assessor.
Table 2: Overview of assessments per visit

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Screening</th>
<th>Baseline</th>
<th>Post-assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAR-Q</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight and height</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Waist and hip circumference</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Transthoracic echocardiography*</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neuropsychological assessment</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Physical fitness (6MWT, VO2max)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Physical activity (activity monitor)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>General functioning (DAD, CDR, iADL)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neuropsychiatric measures</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hemodynamic parameters**</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cerebral parameters**</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Respiratory parameters**</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

MMSE: Mini mental state examination, PAR-Q: Physical activity readiness questionnaire, ECG: electrocardiography, MRI: Magnetic resonance imaging, 6MWT: Six minute walk test, VO2max: Maximum oxygen consumption, DAD: Disability assessment of dementia, CDR: Clinical dementia rating, iADL: Instrumental activities in daily life.

*: Transthoracic echocardiography is only performed in Amsterdam.

**: These parameters are part of the add-on study.

INTERVENTION

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

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 an interval training, based on the 4x4 minutes aerobic interval training model (Figure 2). This type of training has been used in several studies with healthy subjects and various cardiac patients.\textsuperscript{30} The interval training contains 4 cycles of different exercise intensities. Each cycle lasts 7 minutes: 4 minutes of high intensity exercise (85-95% heart rate peak [HR\textsubscript{peak}]), followed by 3 minutes low-to-moderate intensity exercise (60-70% HR\textsubscript{peak}). The intensity of each cycle is individualized for participants using their individual activity level (HR\textsubscript{peak}), assessed during a maximal cardiopulmonary exercise test. The HR is monitored using a 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’s Rating of Perceived Exertion (RPE),\textsuperscript{31} to rate the amount of effort. Furthermore, participants record their ordinary daily physical activities.

![Figure 2: 4x4 minutes aerobic interval training model.](image-url)
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 ergometer at home for 14 weeks after post-assessment as an introduction to aerobic exercise and encouragement to participate in sport activities.

MEASURES

Primary outcome measure
CBF is measured with ASL-MRI, a quantitative and non-invasive 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 (pCASL) to quantify CBF, and 2) multi-phase pseudo-continuous ASL (pCASL) with multiple post-label 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 arterial size, stiffness and the cardiac output fraction. The influence of transit time is of particular interest in patients with altered hemodynamic status, e.g. 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 prior to the MRI, from caffeine and smoking during the preceding six hours and from eating one hour prior to the MRI measurements.

Secondary outcome measures
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 and is designed to cover global cognitive function and four major cognitive domains including memory, attention, language and executive functioning (Table 3). Further, 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.
Table 3: Standardized neuropsychological assessment and measures of daily functioning, neuropsychiatry and Quality of Life

<table>
<thead>
<tr>
<th>Test / questionnaire</th>
<th>Domain(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive functioning</strong></td>
<td></td>
</tr>
<tr>
<td>Mini mental state examination (MMSE)</td>
<td>Global cognition</td>
</tr>
<tr>
<td>15-Word-Auditory Verbal Learning Test (AVLT)*</td>
<td>Episodic memory</td>
</tr>
<tr>
<td>Visual Association Test, short version (VAT)</td>
<td>Implicit associative visual learning</td>
</tr>
<tr>
<td>Digit-Span of the WAIS-III (forward and backward)</td>
<td>Working memory</td>
</tr>
<tr>
<td>Fluency, 60 seconds (animals)</td>
<td>Verbal word fluency / semantic memory</td>
</tr>
<tr>
<td>Letter Digit Substitution Test, 90 seconds (LDST)</td>
<td>Information processing speed</td>
</tr>
<tr>
<td>Stroop Color Word Test</td>
<td>Information processing speed, attention and response inhibition / executive functioning</td>
</tr>
<tr>
<td>Trail Making Test (TMT, part A and B)</td>
<td>Information processing speed, attention and concept shifting / executive functioning</td>
</tr>
<tr>
<td><strong>Daily functioning, neuropsychiatry and Quality of Life</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Dementia Rating (CDR)</td>
<td>Global rating of dementia severity</td>
</tr>
<tr>
<td>Amsterdam iADL</td>
<td>Activities of daily life</td>
</tr>
<tr>
<td>Disability Assessment of Dementia (DAD)</td>
<td>Activities of daily life</td>
</tr>
<tr>
<td>Geriatric Depression Scale-15 (GDS-15)</td>
<td>Depressive symptoms</td>
</tr>
<tr>
<td>Starkstein Apathy Scale</td>
<td>Apathy symptoms</td>
</tr>
<tr>
<td>EuroQol-5D, including EuroQol Visual Analogue Scale</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>Short Stroke-Specific Quality of Life Scale (SS-Qol-12)</td>
<td>Quality of life in patients with stroke</td>
</tr>
</tbody>
</table>

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

**Physical fitness and physical activity**
Cardio-respiratory fitness is assessed by a maximum capacity test (maximal oxygen consumption [VO2max test]) on an electromagnetic bicycle ergometer. Work rate is progressively increased with 10, 15, 20 or 25 Watt (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 10W per minute, for conditioned individuals 20W). Stopping criteria for the VO2max test, as recommended by the American College of Sports Medicine, were physical exhaustion, rounds per minute below 60, or safety reasons. 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, blood pressure is measured every three minutes. In addition, participants perform a 6-minute walk test (6MWT). Both after the VO2max as after the 6MWT, participants are asked to monitor the intensity using Borg’s RPE. Amount, frequency and intensity of physical activity in daily life are monitored by a tri-axial activity monitor (ActiGraph GT3X+, ActiGraph, Pensacola, Florida, USA), which is worn for 7 consecutive days, following screening and post-assessment. The Physical Activity Scale in the Elderly
(PASE) is used to estimate the participants’ physical activity in daily life. This self-report questionnaire is a valid measure of physical activity in older individuals.

**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, HbA1c) and inflammation (i.e. plasma CRP, fibrinogen, IL-1, IL-6, IL-10, s-ST2 and TNF-alpha) 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 creatinin) and remodeling of blood vessel pathology (i.e. plasma homocysteine and endostatin) and of Alzheimer type pathology (i.e. plasma Aß40 and Aß42). Finally, we consider biomarkers which are specifically involved in potential other mechanisms of the effect of the intervention on cognition (i.e. brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) and thyroid-stimulating hormone). Blood samples were collected in a non-fasting 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)) and currently unknown genetic variants that might be involved in risk of cardiovascular disease, and/or cognitive decline.

**Brain structure**

Brain and cardiac (see below) MRI is acquired on Philips Gemini 3T PET-MR scanner in VUmc and Philips Ingenia 3T scanner in 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 gray matter (GM), white matter (WM), cerebrospinal fluid and WMH, and 2) total brain volume, GM and WM volume of 83 structural brain regions (mL; obtained using atlas-based segmentation with the Hammer’s atlas).
**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 post-assessment. 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). Both CBFv and blood pressure are continuously measured in the supine and standing position of the participant.

CVMR is quantified by non-invasive and continuous measurements of CBFv and end-tidal CO₂ (using a nasal cannula) during hyperventilation, normal breathing and normal breathing while inhaling a gas mixture containing 5% CO₂ and 95% O₂ (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 VO₂max, until 70% of maximal HR has been reached.

**Demographic and other baseline variables**

**Clinical data**

Data on risk factors for VCI and relevant co-morbidities are collected, according to the framework of the recent American Heart Association (AHA) position statement on VCI. Non-modifiable risk factors include demographic factors (gender, age, ethnicity). Modifiable risk factors include lifestyle factors (education, physical activity, alcohol use, 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).

**Cardiac MRI**

Cardiac MRI is performed at baseline with electrocardiographic gating and a phased array cardiac receiver coil. Cine images in 2-chamber left, 2-chamber right, 3-chamber, 4-chamber and short-axis views are obtained using a balanced steady-state free precession (bSSFP) pulse sequence in breath-hold. Anatomy and dimensions of the thoracic aorta are visualized using a bSSFP pulse sequence. Free breathing 2D 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 (LV) ejection fraction, cardiac output, LV mass, diastolic dysfunction (E/A ratio mitral inflow), left atrial volume, valve abnormalities and aortic pulse wave velocity.

**Transthoracic echocardiography**

All participants included in 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 non-invasive, harmless and routinely used in cardiac patients.

**STATISTICAL METHODS**

**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 of age, it was concluded that aerobic exercise training is beneficial for cognitive functioning. 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. Based on studies focusing on CBF in patients with dementia, we assume a large effect size of 0.60. This corresponds to a difference in mean change in CBF of 3±5 ml/100mg/min), as was found in a longitudinal study of patients with hypertension, compared to patients without hypertension. 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.

**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 (ANOVA) 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 (WMH, 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 versus 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 $<.05$.

**DISCUSSION**

ExCersion-VCI is part of the Heart-Brain Connection, a national interdisciplinary collaborative network. In this consortium we aim to give insight in 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. Epidemiological 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, due to 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. 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 maybe even preventing ongoing cognitive decline ultimately progressing to dementia in patients with VCI.
APPENDIX

Data collection and storage

Data analysis

Paper clinical rating forms (CRFs) are used to collect non-imaging data according to standard operating forms (SOPs) that are specifically designed for ExCersion-VCI. After pseudonymisation to protect the participants’ privacy, non-imaging data are stored in a central database (OpenClinica, LLC, Waltham, Massachusetts, USA; www.openclinica.com). Blood samples are processed and stored in each local biobank according to a SOP for blood samples. The originals of all source documents are stored for a period of 15 years, in agreement with the Dutch Personal Data Protection Act (in Dutch: de Wet Bescherming Persoonsgegevens).

Imaging data

Imaging data are centrally stored using the Extensible Neuroimaging Archive Toolkit (XNAT), an open source web service for storing and organizing of medical imaging data. TraIT BioMedical Imaging Archive (BMIA) (https://xnat.bmia.nl) hosts the server XNAT. MRI data are anonymized locally using the Clinical Trial Processor (CTP). Image processing results are stored next to the original MRI data on XNAT. Image data quality (completeness, consistency in software version and agreement with scanning protocol) is automatically monitored by a weekly quality assurance (QA) report. The quantitative imaging biomarkers from both brain as cardiac MRI are computed with existing software and software that is specifically designed for the Heart-Brain Connection consortium.
REFERENCES


29. Evans S, Royston P, Day S. No Title.


