Part II
Physical exercise into practice
Safety and feasibility of post-stroke care and exercise after minor ischemic stroke or transient ischemic attack: MotiveS & MoveIT

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ABSTRACT

Background Despite the beneficial effect of cardiac rehabilitation after myocardial infarction, a rehabilitation program to improve cardiorespiratory fitness and influence secondary prevention has not been implemented for ischemic stroke and transient ischemic attack (TIA).

Objective To investigate the safety and feasibility of a post-stroke care including an exercise program after minor ischemic stroke or TIA.

Methods In a randomised controlled trial, 20 patients with a recent minor stroke or TIA without cardiac contraindications were randomly assigned to one of the two interventions; post-stroke care without exercise or post-stroke care with exercise. Patients were evaluated at baseline, 6 and 12 months.

Results Eighteen patients completed the intervention. In none of the patients cardiopulmonary contraindications for the maximal exercise test and exercise program were found. No cardiovascular events occurred during the maximal exercise tests and exercise program. After one year, significantly more patients in the post-stroke care with exercise group achieved the composite endpoint of optimal medical therapy.

Conclusions Post-stroke care including an exercise program is safe and feasible in the acute phase after minor stroke or TIA and might be a way to increase effectiveness of secondary stroke prevention. We are currently conducting a larger trial to validate these results.
INTRODUCTION

Patients with an ischemic stroke or transient ischemic attack (TIA) have an increased risk of recurrent stroke, myocardial infarction and vascular death.\(^1,2\) In these patients evidence for the effectiveness of secondary prevention strategies is compelling. The combination of antithrombotics, blood pressure control, statins, dietary modification, and physical exercise, significantly lowers the risk of recurrent stroke and other future cardiovascular events.\(^3-8\) Despite this convincing evidence, secondary prevention in the daily practice of stroke care is suboptimal.\(^9,10\)

Previously, it has been demonstrated that cardiac rehabilitation including a physical exercise program reduces mortality in patients after myocardial infarction.\(^11\) Furthermore, moderate and high levels of physical activity in primary prevention are associated with a reduced stroke incidence and exercise prior to stroke might improve stroke outcome.\(^4,12\) Despite this demonstrated beneficial effect of physical exercise in primary prevention and after myocardial infarction, a specific rehabilitation program to improve cardiorespiratory fitness and to influence secondary prevention targets has not been implemented for ischemic stroke or TIA.

Several randomized trials investigating the effect of an exercise program in patients in the chronic phase after stroke or TIA have been conducted previously.\(^13-15\) However, these interventions often took place months or years after the initial event and cardiorespiratory fitness itself was not always measured. In this pilot study we studied the safety and feasibility of a post-stroke care program including an exercise program in the acute phase after minor ischemic stroke or TIA. In addition, we investigated the effect of this program on cardiorespiratory fitness and secondary prevention targets.

METHODS

Study design

We conducted a prospective, single-blinded, randomized controlled pilot-study to investigate the safety and feasibility of a post-stroke care program with and without an exercise program in patients in the acute phase after minor ischemic stroke and TIA. Study procedures were approved by local university and hospital research ethics committees. Informed written consent was obtained from all subjects. Consenting subjects were randomly assigned to one of the two interventions; (1) a multidisciplinary post-stroke care program (post-stroke care without exercise) or (2) the same program, including an aerobic exercise program (post-stroke care with exercise) (Figure 1). After randomisation, patients were screened for possible cardiac or pulmonary disease. For this purpose, our study group developed a cardiopulmonary screening test, consisting of items concerning past medical history, disease history, physical and ancillary (electrocardiogram (ECG)) investigations. This screening test was used to detect patients with possible cardiopulmonary contraindications.
for physical exercise. All patients who had a positive cardiopulmonary screening test and those who were randomly assigned to the post-stroke care with exercise group were examined by a cardiologist and pulmonologist before baseline. Primary and secondary endpoints were evaluated at baseline, 6 and 12 months.

20 patients
• minor stroke or TIA
• no known cardiac contra-indications

Randomised
• post-stroke care without exercise
• post-stroke care with exercise

16 patients referred to cardiologist:
• 8 patients: positive item on cardiac checklist
• 8 patients: randomisation in exercise group
conclusion: no contra-indication for exercise program or maximal exercise test

10 patients: post-stroke care without exercise
1 patient: not motivated
1 patient: cardiac complaints
10 patients: post-stroke care with exercise
8 patients: completed the program

Figure 1 Flowchart summarizing the progress of the pilot study

Patients
From June 2010 until October 2010, 20 consecutive, consenting patients were recruited from the neurology department in the Sint Lucas Andreas Hospital in Amsterdam. Patients were eligible if they (1) were at least 18 years old, (2) presented with a minor ischemic stroke or TIA defined as National Institutes of Health Stroke Scale (NIHSS) score ≤ 316 (3) with an onset of signs and symptoms less than one week ago, (4) were able to walk independently and (5) were discharged without need for further rehabilitation. Patients were excluded if they had (1) dementia or a Mini Mental State Examination (MMSE) score < 24, (2) aphasia or language barrier, (3) cardiopulmonary contra-indication for physical exercise and exercise testing outlined by the American College of Sports Medicine (ACSM)17 or (4) chronic disease with an expected survival less than 2 years.
Interventions

Post-stroke care program: during this one-year program patients visited our outpatient clinic at 4 weeks, 3 months, 6 months and 9 months after the index event. The program consisted of a stepwise approach to lower blood pressure and LDL-cholesterol (LDL-c) levels with pharmacological therapy and an on motivational interviewing based counselling strategy. This counselling strategy aimed to motivate patients to attain a healthy and active lifestyle and optimize medication adherence. The stepwise approach was documented in a protocol and distributed to all participating physicians, nurses and physiotherapists, who were all trained in and qualified for motivational interviewing.

Exercise program: patients participated in an 8-week aerobic exercise program. During this period patients had three one-hour exercise sessions a week supervised by two specialized physiotherapists. These sessions consisted of aerobic exercise and strength training. The exercise intensity was based on the maximal heart rate and the maximal power achieved during the maximal exercise test. During the program the exercise intensity was gradually increased. After the exercise program, patients were seen by a physiotherapist every 3 months in the outpatient clinic to motivate them to maintain an active lifestyle.

Primary outcome measures

Safety and feasibility: safety was assessed by registering all adverse events during the study. In addition, all new vascular events were recorded. The feasibility was determined by the number of patients who completed the intervention and follow-up period of one year.

Secondary outcome measures

Maximal exercise capacity: maximal exercise capacity (VO2max), or maximal oxygen consumption in milliliter per kilogram per minute (ml/kg/minute), was used as the measure of cardiorespiratory fitness. A symptom-limited ramp exercise test was performed on a Jaeger cycle ergometer. During these tests continuous electrocardiographic monitoring was performed and the blood pressure was measured every minute. Oxygen consumption (VO2) was continuously measured using a metabolic measurement system, which performed breath-by-breath gas analysis (Oxycon Pro, Jaeger). The testing protocol was adjusted to the capabilities of the patient. Exercise was terminated if patients were fatigued or earlier when fulfilling the ACSM’s guidelines ‘Indications for terminating Exercise Testing’. The results were reviewed by a cardiologist and pulmonologist. The maximal value obtained was considered the VO2max.

Measures of secondary prevention: secondary prevention was measured as the number of patients who achieved the composite endpoint of optimal medical therapy, defined as the combination of prescribed antithrombotic therapy (antiplatelet agents or oral anticoagulants)
and achievement of both blood pressure (< 140/90 mmHg) and LDL-c (< 100 mg/dL) targets. These cut-off points were based on current guidelines. Other endpoints were the individual components of the composite endpoint of optimal medical therapy, medication adherence (Morisky medication adherence scale), number of patients not smoking (self reported), alcohol consumption (self reported), body mass index (BMI) and waist circumference.

Statistical analysis
Data were analysed using SPSS. We performed the Mann-Whitney U test for non-parametric continuous data and \( \chi^2 \) analyses for categorical data on baseline characteristics. We measured the differences between baseline, 6 and 12 months for the continuous data and performed the Mann-Whitney U test to detect differences between the groups. We performed logistic regression for the outcome measures with a dichotomous outcome and corrected for baseline values.

RESULTS
Primary outcome measures
Safety and feasibility: the characteristics of the 20 included patients were not significantly different between both groups at baseline (Table 1). As a result of the cardiopulmonary screening, 16 patients were seen by the cardiologist and 15 patients by the pulmonologist. The consultation of the cardiologist and pulmonologist, including cardiac exercise testing, Holter telemetry and/or echocardiography, took several weeks. Therefore, the start of the post-stroke care with exercise program took place after a median of 12 weeks (range 7–24 weeks) after the initial event.

The post-stroke program including an exercise program was safe. No cardiac or pulmonary contraindications for the maximal exercise test and exercise program were found and no cardiovascular events occurred during the maximal exercise tests and exercise program. Twenty patients performed 58 maximal exercise tests during the follow-up period. During five maximal exercise tests transient ECG abnormalities occurred in five patients. After consultation of a cardiologist in one patient no ancillary investigations were required. Three patients underwent a myocardial perfusion scan, which revealed no abnormalities. The last patient, who was randomised in the post-stroke care without exercise group, underwent a percutaneous coronary intervention because of symptomatic coronary artery disease, which was supported by ECG abnormalities during the maximal exercise test. During follow-up three additional vascular events occurred. In the post-stroke care with exercise group one patient had a TIA and one patient had a minor stroke. In the post-stroke care without exercise group one patient had a TIA.
Safety and feasibility of exercise after minor stroke or TIA

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>post-stroke care without exercise</th>
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<tr>
<td>patients (n)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>male (n)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>age (mean, range)</td>
<td>63.0 (46–78)</td>
<td>62.4 (46–73)</td>
</tr>
<tr>
<td>stroke (n)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>TIA (n)</td>
<td>3</td>
<td>5</td>
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<tr>
<td>NIHSS (median, range)</td>
<td>1 (0–3)</td>
<td>0 (0−2)</td>
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<tr>
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<td>hypertension (n)</td>
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<td>155/82 mmHg</td>
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<td>LDL-c (mean)</td>
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<td>1</td>
</tr>
<tr>
<td>history of CVD (n)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>history of stroke (n)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>MMSE (median, range)</td>
<td>29.5 (28–30)</td>
<td>28.5 (24–30)</td>
</tr>
<tr>
<td>VO2max (median, range)</td>
<td>20.8 (12.9–30.1)</td>
<td>22.9 (11.9–45.4)</td>
</tr>
</tbody>
</table>

NIHSS = NIH Stroke Scale; AF = atrial fibrillation; LDL-C = LDL-cholesterol; CVD = cardiovascular disease; MMSE = Mini Mental State Examination; VO2max = maximal oxygen consumption in ml per kg per minute.

The post-stroke program including an exercise program was also feasible, since all patients completed the follow-up of one year and eighteen patients completed the intervention. Two patients in the post-stroke care with exercise group did not complete the intervention. One patient declined to participate due to lack of motivation and the second patient had to stop during the exercise program due to pre-existent cardiac disease and inability to perform physical activity (Figure 1).

Secondary outcome measures

Maximal exercise capacity: patients had a median maximal exercise capacity of 22ml/kg/min at baseline, which is lower than the 10th percentile of age- and sex related normative values (Table 1).17 At 6 months the exercise capacity increased slightly, although non-significant, in the post-stroke care with exercise group (median change VO2max 1.6 ml/kg/min) and remained stable in the post-stroke care without exercise group (median change VO2max 0.5 ml/kg/min) (Figure 2). At 12 months this effect disappeared. This was at least partially explained by recent operations in two patients before the last evaluation in the post-stroke care with exercise group and thus lower exercise capacity scores; one
patient had a total hip replacement; the other patient underwent surgery for colon cancer (Figure 2).

Figure 2 Cardiorespiratory fitness of patients at baseline, 6 months and 12 months. Data presented per group, every line representing a single patient. VO2max = maximal oxygen consumption in ml per kg per minute.

Measures of secondary prevention: overall, after 12 months 45% of the total number of 20 patients reached the composite endpoint of optimal therapy. In the post-stroke care with exercise group 7 of 10 patients achieved this combined target versus 2 of 10 in the post-stroke care without exercise group, a significant difference (odds ratio (95% confidence interval) 9.1 (1.1–73.8), \( p = 0.04 \)) (Table 2). This was mainly attributed to a significantly higher number of patients who achieved the target for LDL-c after 12 months. Mean blood pressure measurements and mean LDL-c levels were non-significantly lower in the post-stroke care with exercise group compared with the post-stroke care without exercise group at 12 months. No significant differences were found between both groups in the rate of smoking cessation, alcohol consumption, medication adherence, BMI and waist circumference after 12 months.
Table 2 Secondary prevention targets after 12 months

<table>
<thead>
<tr>
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<th>post-stroke care without exercise</th>
<th>post-stroke care with exercise</th>
<th>P value</th>
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<tr>
<td>patients (n)</td>
<td>10</td>
<td>10</td>
<td></td>
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<td>optimal therapy (n)</td>
<td>2</td>
<td>7*</td>
<td>0.038</td>
</tr>
<tr>
<td>use of antithrombotics (n)</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>blood pressure ≤ 140/90 mmHg (n)</td>
<td>8</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>blood pressure (mean)</td>
<td>127/75 mmHg</td>
<td>120/71 mmHg</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-c ≤ 100 mg/dl (n)</td>
<td>3</td>
<td>8*</td>
<td>0.037</td>
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<tr>
<td>LDL-c (mean)</td>
<td>98.6 mg/dl</td>
<td>82.0 mg/dl</td>
<td>NS</td>
</tr>
</tbody>
</table>

Optimal therapy = the combination of prescribed antithrombotic therapy and achievement of both blood pressure (< 140/90 mmHg) and LDL-c (< 100 mg/dl) targets; LDL-c = LDL-cholesterol; NS = non significant.

DISCUSSION

In this pilot study we have demonstrated that in the acute phase after a minor ischemic stroke or TIA post-stroke care including an exercise program, similar to cardiac rehabilitation, is safe and feasible. Improving adherence to guidelines and lifestyle changes by such a program might be a way to increase effectiveness of secondary stroke prevention.

No cardiopulmonary contra-indications for physical exercise were found and no cardiovascular events occurred during the maximal exercise tests and the exercise program. All patients completed the follow-up of one year and eighteen patients completed the intervention. Since cardiopulmonary analysis revealed no contraindications for physical exercise and no cardiovascular events occurred during the maximal exercise tests and exercise program, the developed cardiopulmonary screening test seems to be a useful instrument to detect concomitant cardiac disease that could lead to complications during physical exercise. Therefore, this cardiopulmonary screening test is currently used in our clinical stroke practice.

Several randomized trials investigating the effect of an exercise program on cardiorespiratory fitness in patients with a stroke or TIA months or years after the initial event have been conducted previously. However, there is not much experience with exercise interventions in the acute phase after minor stroke or TIA. A previous randomised trial by Duncan et al, found that an exercise program in 92 patients in the subacute phase after major stroke was safe and feasible and improved the cardiorespiratory fitness. In our study the exercise capacity did not increase significantly after 6 and 12 months in the post-stroke care with exercise group. Our pilot was not powered to detect the increase of 10% in maximal exercise capacity, which is normally observed. Apart from our pilot study, only one small, randomized controlled trial has been performed in 28 patients in the acute phase after minor stroke or TIA. However, in this trial cardiorespiratory fitness was not measured.
Interestingly, we found that at baseline most patients had a low exercise capacity, sometimes not even exceeding the accepted minimal value of 15 ml/kg/min meeting the physiological demands of independent living.\textsuperscript{20} In addition, the low median VO2 max in our patients was close to the 21 ml/kg/min level, which in previous studies has been associated with an increased mortality among patients with coronary artery disease.\textsuperscript{21} It is remarkable that patients who have suffered an ischemic stroke with no or small neurological deficit or a TIA can have such a low maximal exercise capacity. It seems likely that low cardiorespiratory fitness after stroke is due, at least in part, to low premorbid cardiorespiratory fitness that is attributable to health-, lifestyle- and age-related declines.

It has been suggested that cardiac comorbidity herein plays a central role. After a stroke some patients are more disabled by associated cardiac disease than by the stroke itself.\textsuperscript{22} Therefore, our results suggest that the importance of improvement of cardiorespiratory fitness is currently underestimated in stroke rehabilitation.

In the earlier mentioned studies less attention was given to secondary prevention targets. In our study, a significant larger proportion of patients in the post-stroke care with exercise group reached the composite endpoint of optimal therapy in comparison with the post-stroke care without exercise group. The effect on achievement of LDL-c targets explained the difference for the greatest part. This is in accordance with a previous study, performed in patients with a history of stroke, which demonstrated an effect of physical exercise on cholesterol levels.\textsuperscript{23} In addition, Prior et al performed a prospective cohort study of 100 patients, who after a mean duration of 12 weeks after stroke, participated in a cardiac rehabilitation program in collaboration with a stroke prevention clinic.\textsuperscript{24} After six months they found a significant improvement in blood lipid profiles with significant decreases in total cholesterol and triglycerides levels and a significant shift toward self-reported abstinence from smoking.\textsuperscript{24} However, it remains uncertain whether there is a causal relation between physical exercise and cholesterol levels. Further randomized studies are needed to assess and replicate the effects of post-stroke care including an exercise program on secondary prevention targets after ischemic stroke or TIA. In conclusion, post stroke care including an exercise program is safe and feasible in the acute phase after minor ischemic stroke or TIA and could be beneficial for secondary prevention.
REFERENCES


A randomised controlled trial of aerobic exercise after transient ischemic attack or minor stroke to prevent cognitive decline: the MoveIT study protocol.
ABSTRACT

Introduction Patients with transient ischemic attack (TIA) or stroke are at risk for cognitive impairment and dementia. Currently, there is no known effective strategy to prevent this cognitive decline. Increasing evidence exists that physical exercise is beneficial for cognitive function. However, in patients with TIA or stroke who are at risk for cognitive impairment and dementia, only a few trials have been conducted. In this study, we aim to investigate whether a physical exercise program (MoveIT) can prevent cognitive decline in patients in the acute phase after a TIA or minor ischemic stroke.

Methods and analysis A single-blinded randomised controlled trial will be conducted to investigate the effect of an aerobic exercise program on cognition compared with usual care. 120 adult patients with a TIA or minor ischemic stroke less than one month ago will be randomly allocated to an exercise program consisting of a 12-week aerobic exercise program and regular follow-up visits to a specialised physiotherapist during the period of one year or to usual care. Outcome measures will be assessed at baseline, one and two-year follow-up. The primary outcome is cognitive functioning measured with the Montreal Cognitive Assessment (MoCA) and with additional neuropsychological tests. Secondary outcomes include maximal exercise capacity, self-reported physical activity, and measures of secondary prevention.

Ethics and dissemination The study received ethical approval from the Medical Ethical Review Committee of VU University Medical Center (VUmc), Amsterdam (2011/383). The results of this study will be published in peer-reviewed journals and presented at international conferences. We will also disseminate the main results to our participants in a letter.

Clinical Trial Registration Number Nederlands Trial Register NTR3884
INTRODUCTION

Patients with transient ischemic attack (TIA) or ischemic stroke have an increased risk of developing cognitive impairment and dementia.\textsuperscript{1,2} Cognitive impairment not only occurs in patients with major stroke, but also in patients after TIA or minor stroke.\textsuperscript{3-5} In a meta-analysis of 7511 patients, 10% developed new dementia after first stroke, and more than a third had dementia after recurrent stroke.\textsuperscript{1} In patients with stroke, the prevalence of mild cognitive impairment varies between 20 and 90%.\textsuperscript{5,6} In addition, multiple studies demonstrated that the occurrence of cognitive impairment or dementia after stroke predicts death and dependency.\textsuperscript{7-10} Currently, there is no known effective strategy to prevent cognitive decline or dementia in these patients.

Physical activity has been associated with a decreased risk for dementia and cognitive decline.\textsuperscript{11,12} In healthy elderly individuals, there is evidence that a physical exercise program is associated with an improvement in cognitive performance.\textsuperscript{13} Current stroke guidelines advise at least 30 minutes of moderate-intensity physical exercise 3 to 7 times a week, for patients with TIA or ischemic stroke who are capable of engaging in physical activity.\textsuperscript{14} For patients after myocardial infarction, a physical exercise program is standard care and a part of cardiac rehabilitation, and this exercise program is associated with a reduced mortality.\textsuperscript{15}

In patients with vascular disease, conflicting results have been found with regard to the association between physical activity and cognition. One cohort study found that physical activity was associated with better preservation of cognitive function,\textsuperscript{16} another more recent study could not confirm this association.\textsuperscript{17} Until now, three observational studies and only one randomised controlled trial have assessed the effect of a physical exercise program on cognition in patients with a TIA or stroke.\textsuperscript{18-21} This randomised controlled trial only included patients who had a stroke more than 6 months ago and found an improvement in motor learning.\textsuperscript{19} No randomised controlled trials have been performed in the acute phase following a TIA or stroke.

Previously, we demonstrated the safety and feasibility of an exercise program in the acute phase after a TIA or a minor ischemic stroke.\textsuperscript{22} The aim of this larger study is twofold; (1) to investigate whether a physical exercise program (MoveIT) can prevent cognitive decline in patients after a TIA or minor ischemic stroke and (2) to investigate the effect of this program on cardiorespiratory fitness and the attainment of secondary prevention targets.

METHODS AND ANALYSIS

Study design and setting

MoveIT is a two parallel group, single-centre, single-blinded, randomised controlled trial to investigate the effects of an aerobic exercise program on cognition in patients in the acute phase after TIA or minor ischemic stroke (Figure 1). The study will be conducted in the Sint Lucas Andreas Hospital, a district hospital in Amsterdam with a specialised stroke
unit. Participants will be randomly assigned to a control or intervention group. The control group will receive the usual care for patients after TIA or minor ischemic stroke, consisting of two or three visits to the outpatient clinic. The intervention group will participate in the MoveIT program, which consists of a 12-week aerobic exercise program and follow-up visits to a specialised physiotherapist every 3 months during the period of one year. Study procedures were approved by local university and hospital research ethics committees. Informed written consent will be obtained from all participants. The study has been registered at the trial registration (Nederlands Trial Register – NTR3884).

Objectives

**Primary objective:**
To investigate the effect of a physical exercise program (MoveIT) on cognition in patients in the acute phase after a TIA or minor ischemic stroke, compared with participation in usual care.

**Secondary objectives:**
- to investigate the effect of a physical exercise program on cardiorespiratory fitness, measured by maximal exercise capacity.
- to investigate the effect of a physical exercise program on the attainment of secondary prevention targets, defined as the combination of prescribed antithrombotic therapy (antiplatelet agents or oral anticoagulants) and achievement of blood pressure (< 140/90 mmHg) and low-density lipoprotein cholesterol (LDL-c; < 100 mg/dL) targets, as recommended in international guidelines.²³

Participants

**Inclusion criteria**
Patients are eligible if they (1) are at least 18 years old, (2) present with a TIA or minor ischemic stroke defined as National Institutes of Health Stroke Scale (NIHSS) score ≤ 3,²⁴ (3) had the onset of signs and symptoms less than 1 month ago, (4) are able to walk independently and (5) are discharged from hospital without need for further rehabilitation.

**Exclusion criteria**
Patients will be excluded if they have (1) dementia or a Mini-Mental State Examination (MMSE) score < 24, (2) aphasia or the inability to speak Dutch, (3) cardiopulmonary contraindication for physical exercise and exercise testing outlined by the American College of Sports Medicine (ACSM)²⁵ or (4) chronic disease with an expected survival less than 2 years.
Recruitment

Consecutive patients with a TIA or a minor ischemic stroke admitted to the stroke unit or evaluated in the outpatient clinic or emergency room of the Sint Lucas Andreas Hospital will be given information about the trial. Patients who are interested to participate will be approached with further information and screened for cardiac contraindication using a cardiac checklist. This cardiac checklist has been developed by our study group and consists of items concerning the patient’s medical history, disease history, physical and ancillary...
(ECG) investigations. Before randomisation, all potential participants with a positive cardiac checklist will be examined by a cardiologist to exclude possible cardiac contraindication for maximal exercise testing or a physical exercise program. After exclusion of cardiac contraindications or a negative cardiac checklist, written informed consent will be obtained. If there are indications of pulmonary disease, patients will be referred to a pulmonologist to optimise the pulmonary function prior to the start of the program.

**Randomisation**

Consenting participants will be allocated for treatment using block randomisation with a block size of two. The allocation sequence will be generated by coin tossing. Randomisation will be conducted independently using sealed opaque envelopes.

**Intervention**

Participants randomly assigned to the intervention group will participate in the MoveIT program. This program consists of a 12-week aerobic exercise program, combined with regular follow-up visits to a specialised physiotherapist during the period of one year. During the aerobic exercise program, participants will receive two 1 h exercise sessions per week supervised by two specialized physiotherapists. These sessions consist of aerobic exercise and strength training. The exercise intensity will be based on the individual’s maximal heart rate and the maximal power achieved during the maximal exercise test. During the program, the exercise intensity will gradually be increased. Participants will start with home-based aerobic exercise and will gradually increase this frequency to three times a week. Participants will keep a log of these activities and will discuss their progress with the physiotherapists during the exercise sessions and during the follow-up visits after the completion of the exercise program.

After the completion of the physical exercise program, follow-up consists of a total of three visits to the physiotherapist during the period of one year. During these appointments, participants will receive motivational interviewing-based counselling by physiotherapists in order to motivate them to maintain an active lifestyle. Participating physiotherapists received a motivational interviewing training and have considerable experience with this technique.

**Control group**

Participants in both groups will continue to receive usual stroke care. Usual care consists of a total of 2–3 follow-up visits to the outpatient clinic for 3 months after the TIA or stroke. During these appointments, the motivational interviewing-based counselling will be focussed on the attainment of secondary prevention and the improvement of lifestyle factors and physical activity.
Data collection and outcomes measures

Outcome measures will be assessed at baseline, one and two-year follow-up by personnel blinded to the treatment allocation. Data will be recorded on standardised forms and entered into a secured Access database with Structured Query Language (SQL) that contains quality control checks (e.g., range checks, notification of missing data).

Cognitive functioning

The primary endpoint is global cognitive functioning measured using the Montreal Cognitive Assessment (MoCA) test, which has been validated to measure cognitive decline in patients after stroke.

In addition, a standardised neuropsychological examination will be performed which consists of attention, verbal and visual memory and executive functioning tests. Verbal memory will be assessed using the Dutch version of the California Verbal Learning Test (VGLT). Non-verbal memory will be assessed with the recall of the Rey-Osterrieth Complex Figure Test. Executive functioning will be assessed using the Key Search and Rule Shift Cards from the Behavioural Assessment of the Dysexecutive Syndrome (BADS), letter fluency and categorical fluency, difference in time between part A and B of Trail Making Test, the interference score of the Stroop Color Word Test, and the Stop Signal Task of the CANTAB. Attention will be assessed with the digit span forwards and backwards of the Wechsler Adult Intelligence Scale (WAIS). In addition, participants will fill out a validated questionnaire measuring cognitive complaints (Cognitive Failures Questionnaire).

Baseline composite z-scores for the cognitive domains: attention, memory and executive functioning will be calculated by averaging the z-scores (raw individual test score at baseline minus the mean test score divided by the standard deviation). Follow-up-composite z-scores will be calculated for the cognitive domains: attention, memory and executive functioning by averaging the z-scores (raw individual test score at follow-up minus mean baseline test score divided by the standard deviation of the baseline test score). These composite z-scores will be used in the further analysis.

Measures of physical function

Maximal exercise capacity (VO2max) or maximal oxygen consumption (ml/kg/minute) is used as the measure of cardiorespiratory fitness. A symptom-limited ramp exercise test will be performed on a Jaeger cycle ergometer. During these tests, continuous ECG monitoring will be performed and the blood pressure will be measured every minute. Oxygen consumption (VO2) will be continuously measured using a metabolic measurement system, which is performed by a breath-by-breath gas analysis (Oxycon Pro, Jaeger). The testing protocol will be adjusted to the capabilities of the patient. Exercise will be terminated if participants are fatigued or earlier if they fulfil the ACSM’s guidelines for ‘Indications for
terminating Exercise Testing. A cardiologist and pulmonologist will review all results of the exercise tests. In case of ECG-abnormalities, a cardiologist will examine the participant to exclude cardiac disease. The maximal value obtained will be considered as the VO2max.

The amount of self-reported physical activity will be measured using the Physical Activity Scale for the Elderly (PASE) questionnaire. This questionnaire has also been validated for the elderly patients in the Dutch population.

Measures of secondary prevention
Secondary prevention will be measured as the number of participants who achieve the composite endpoint of optimal medical therapy, defined as the combination of prescribed antithrombotic therapy (antiplatelet agents or oral anticoagulants) and achievement of both blood pressure (< 140/90 mmHg) and LDL-c (< 100 mg/dL) targets. These cut-off points are based on current guidelines. Other endpoints are the individual components of the composite endpoint of optimal medical therapy, number of participants not smoking (self-reported), alcohol consumption (self-reported), body mass index and waist circumference.

Recurrent vascular events
All recurrent vascular events during the follow-up period of 2 years will be recorded. The trial is not sufficiently powered to determine the effect of the MoveIT program in reducing recurrent TIA, stroke or cardiac events. Thus, it will be exploratory in this regard.

Other
Mental health and fatigue will be assessed using the Hospital Anxiety and Depression Scale (HADS) and the Fatigue Severity Scale.

Covariates
Imaging
At baseline, in all participants a non-contrast head CT-scan will be performed as part of their routine stroke workup. In addition, in all participants without contraindications, a brain MRI will be performed after informed consent. The MR investigations will be performed on a 1.5-Tesla scanner. The protocol consisted of sagittal T1-weighted (repetition time (TR)/echo time (TE): 1940/3.08 ms), sagittal fluid-attenuated inversion recovery (TR/TE 6000/358 ms), transversal T2-weighted (TR/TE 5000/96 ms), transversal T2 weighted gradient echo (TR/TE 800/26 ms) and diffusion-weighted imaging (TR/TE 4100/102 ms). Imaging will be used to evaluate markers of small vessel disease, brain atrophy and carotid calcifications.
Apolipoprotein E
APOE genotype, a genetic risk factor for Alzheimer disease, will be performed after DNA isolation from 10 ml EDTA blood by using the LightCycler® APOE mutation detection method (Roche Diagnostics GmbH) and coded as APOE ε4 or no ε4.

Other
Pre-existent cognitive impairment will be assessed using the Informant Questionnaire for Cognitive Decline in Elderly (IQCODE). Premorbid intellectual functioning will be assessed using the Dutch version of the National Adult Reading Test (DART).

Power calculation and sample size
Global cognition, assessed with the MoCA test, was selected as the outcome variable to calculate sample size. Using estimates obtained from the literature and our previously performed pilot study, a sample size of 52 patients in each group is needed to reach a power of 80% to detect a difference in means in the MoCA score of 1.5 point, assuming a standard deviation of 2.7 using a two-sample t test with a 0.05 two-sided significance level. We increased the sample size to 60 patients in each group to anticipate for potential dropouts.

Analysis
Baseline demographic and clinical characteristics of participants in the intervention and control groups will be compared using two-sample t tests (continuous data) and Chi-square analysis (nominal data). Non-parametric methods will be used when assumptions of normality are violated.

Primary analyses will be unadjusted, following the intention-to-treat principle. For the primary endpoint, the change in MoCA between baseline and 2-year follow-up will be calculated. Depending on the normality distribution, the change scores will be compared using either Wilcoxon rank-sum tests or two-sample t tests with significance level of 0.05.

In the secondary analyses, we will assess the effect on our secondary outcome measures. We will calculate the change between baseline and 2 years continuous data, and this change score will be analysed using either Wilcoxon rank-sum tests or two-sample t tests. We will perform logistic regression for the outcome measures with a dichotomous outcome, such as attainment of measures for secondary prevention using the data at 2-year follow-up as the dependent variable and correcting for baseline using the baseline data as covariate.

A repeated-measures mixed design will be used to estimate the treatment effects (2 groups at 3 time points), using the variables measured at baseline, 1-year and 2-year follow-up, that conform to the assumptions of normality. Level of significance will be < 0.05. Data will be analysed using SPSS (version 20.0).
Chapter 7

ETHICS AND DISSEMINATION

All minor and major amendments to the protocol will be approved by the Ethics committee. A signed and dated informed consent form will be required from all participants. The risks and benefits of participation will be explained and all potential participants are free to decline to participate in the trial. All patient-level data accessed in this study will be stripped of personal identifiers. To guarantee the confidentiality of the participants, only the authors will have access to the data during the study.

We will disseminate the results of our study via presentations at international conferences and publications in peer-reviewed journals.
REFERENCES


Cardiorespiratory fitness after transient ischemic attack and minor ischemic stroke; baseline data of the MoveIT study

H Myrthe Boss
Inger A Deijle
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ABSTRACT

Background Cardiorespiratory fitness (CRF) is reduced in patients with stroke. It is unclear whether it is also reduced in patients with a transient ischemic attack (TIA) or minor stroke. We investigated the CRF in patients with a recent TIA or minor stroke and explored which determinants are associated with a lower fitness.

Methods In 113 patients with a recent TIA or minor ischemic stroke (64 (SD = 10) years of age; 49 (IQR 27–86) days post TIA or stroke), the peak oxygen consumption (VO2peak) was determined in a symptom-limited ramp exercise test. Physical activity level, vascular risk factors, history of vascular or pulmonary disease and stroke characteristics were recorded at inclusion and related to the VO2peak.

Results Mean VO2peak was 22ml/kg/min (SD = 6), which is the fifth percentile of age- and sex-related normative values. Increasing age and female sex were associated with a lower VO2peak (B (95%CI): per 10 years -2.57 ml/kg/min (-3.75; -1.40) and female sex -5.84 ml/kg/min (-8.06; -3.62)). Age- and sex-adjusted linear regression analyses showed that a history of cardiovascular disease and pulmonary disease was associated with a lower VO2peak. In addition, a lower level of physical activity, hypertension, smoking and overweight were associated with a lower VO2peak. History of stroke and stroke characteristics were not related to VO2peak.

Conclusion The majority of patients with a recent TIA or minor ischemic stroke have a poor CRF. Our findings suggest that premorbid cardiovascular and pulmonary disease and vascular risk factors, but not TIA- or stroke-related factors contribute to a reduced CRF.
Fitness after TIA and minor stroke

INTRODUCTION

In patients with a disabling stroke, cardiorespiratory fitness (CRF), measured with the peak oxygen consumption in milliliter per kilogram per minute (VO2peak), is reduced, both in the subacute and the chronic phase after stroke. In 3 studies performed in patients in the subacute phase after a disabling stroke, values for the VO2peak ranged between 12 and 18 ml/kg/min, which is lower than 60% of age- and sex-related normative values. These values may have clinical impact as the accepted minimal value necessary for independent living is estimated at 15 ml/kg/min and values below 21 ml/kg/min have been associated with an increased mortality among patients with coronary artery disease (CAD). In the general population, values lower than the 20th percentile of age and sex, an indicator of a sedentary lifestyle, are also associated with increased all-cause mortality.

The determinants responsible for the reduced CRF after stroke have not yet been elucidated. Both stroke-related factors and a low premorbid fitness attributable to health-, lifestyle- and age-related declines probably influence CRF. It has been suggested that cardiac comorbidity plays a central role in the reduced exercise capacity, as about one fifth of patients after stroke also have asymptomatic CAD. Significant associations between VO2peak and the Barthel index, Fugl-Meyer test, and the Berg Balance Scale have been found, indicating that less disabled persons have a better CRF. Higher age and female sex have also been associated with a lower exercise capacity.

Until now, most studies have been performed in patients in the subacute phase after disabling stroke. It is conceivable that in patients with a TIA or a non-disabling ischemic stroke, stroke-related impairment will play a smaller role in low CRF than in patients who suffered from a disabling stroke. Data on CRF and its determinants in patients with a recent TIA or minor ischemic stroke are lacking. This study aimed to investigate CRF in patients with a recent TIA or minor ischemic stroke and to explore the possible determinants associated with CRF in these patients.

METHODS

Participants

Data were retrieved from the baseline assessment of the MoveIT-study, a randomized controlled trial investigating the effects of an aerobic exercise program on cognition in patients with a recent TIA or minor ischemic stroke. Details of the design of this study have been described elsewhere. Study procedures were approved by the local university and hospital research ethics committee. Written informed consent was obtained from all participants. The study was registered at the Dutch trial registration (Nederlands Trial Register – NTR3884).

In brief, between May 2012 and July 2014 120 adult patients with a TIA or minor ischemic stroke defined as National Institutes of Health Stroke Scale (NIHSS) score less...
than or equal to 3,\textsuperscript{15} with an onset of signs and symptoms less than one month ago and the ability to walk independently, were included. Exclusion criteria were (1) dementia or a Mini-Mental State Examination (MMSE) score less than 24, (2) aphasia or inability to speak Dutch, (3) cardiopulmonary contra-indication for physical exercise and exercise testing as outlined by the American College of Sports Medicine (ACSM)\textsuperscript{16} or (4) chronic disease with an expected survival less than 2 years.

Patients were screened for cardiac contraindications using a checklist that included history of cardiac disease, symptoms of current cardiac disease and results of electrocardiogram (ECG). Before enrollment, all patients with a positive checklist were examined by a cardiologist to exclude cardiac contraindications for maximal exercise testing or a physical exercise program.

Cardiorespiratory fitness
The peak exercise capacity (VO\textsubscript{2peak}), or peak oxygen consumption in milliliter per kilogram per minute (ml/kg/min), was used as the measure of CRF.\textsuperscript{17} A symptom-limited ramp exercise test was performed on a Jaeger cycle ergometer. During the test, continuous electrocardiographic monitoring was performed and the blood pressure was measured every minute. Oxygen consumption (VO\textsubscript{2}) was continuously measured using a metabolic measurement system, which performed breath-by-breath gas analysis (Oxycon Pro, Jaeger). The testing protocol was adjusted to the capabilities of the patient.\textsuperscript{16} Exercise was terminated if participants were fatigued or earlier when fulfilling the ACSM’s guidelines ‘Indications for terminating Exercise Testing’.\textsuperscript{16} A cardiologist and pulmonologist reviewed all results of the exercise tests. In case of ECG-abnormalities, a cardiologist examined the participant to diagnose or exclude cardiac disease. The maximal VO\textsubscript{2} value obtained was considered the VO\textsubscript{2peak}. Other descriptive measures of exercise testing were maximal workload, peak heart rate, and Borg’s 15-point Ratings of Perceived Exertion scale\textsuperscript{18} a scale of 15 point to measure subjective exertion. The use of beta-blocker medication was recorded.

Clinical characteristics
Clinical characteristics included demographic characteristics, medical history and risk factors for vascular disease (smoking, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, body mass index (BMI) and premorbid physical activity) and stroke characteristics. Hypertension was defined as blood pressure lowering drug use or a blood pressure at baseline assessment higher than 140/90 mmHg. Hyperlipidemia was defined as low-density lipoprotein cholesterol level higher than 2.5 mmol/L or lipid lowering drug use at inclusion. Height and weight were measured and the body mass index (BMI) was
calculated (kg/m²). The amount of self-reported physical activity was measured using the Physical Activity Scale for the Elderly (PASE) questionnaire. Stroke characteristics included the type (TIA or minor ischemic stroke), the severity of neurological deficits using the NIHSS and the possible etiology. The etiology categories were a lacunar syndrome based on clinical criteria, a stenosis of the carotid or vertebral artery of more than 50% in the presumed symptomatic vascular territory or cardioembolic. In patients with no clinical lacunar syndrome, stenosis of greater than 50% or cardioembolism the etiology was defined as undetermined.

**Statistical analysis**

Descriptive statistics were used to characterize the subjects and exercise test results. VO₂peak levels were compared with age- and sex-related normative values derived from the Cooper Institute. Research using these data suggests that a VO₂max below the 20th percentile is associated with an increased all-cause mortality. To explore the different determinants associated with VO₂peak, linear regression analysis adjusted for age and sex was used. We estimated the associations of stroke characteristics, medical history and vascular risk factors with VO₂peak. To investigate whether the observed associations between the determinants and VO₂peak were explained by the severity of the other underlying disease, we performed an additional analysis excluding patients with a history of CAD, other vascular disease such as peripheral artery disease (PAD) or chronic obstructive pulmonary disease (COPD) (n = 22).

**RESULTS**

A total of 122 patients were assessed for eligibility in the MoveIT study (Figure 1). Two patients were not included after the cardiologic assessment because of failure to complete the assessment or contraindications for physical exercise. After inclusion of 120 patients, there were 3 drop-outs and 1 participant was excluded because he did not have a TIA or minor stroke. In 3 participants, no maximal exercise test could be performed due to leg complaints or anxiety caused by the mask used to measure the maximal oxygen consumption. After a median of 49 days post TIA or minor stroke (interquartile range 27–86 days), a maximal exercise test was performed in 113 participants (Figure 1). The baseline characteristics of the participants are presented in Table 1. The mean maximal exercise capacity was 22 ml/kg/min, which is the 5th percentile of age- and sex-related normative values. In 88% of the participants the level of fitness was very poor (less than 20th percentile of age and sex-related normative values).
Characteristics of exercise testing are presented in Table 2. Reasons to stop the maximal exercise test were fatigue or complaints of the legs (41%), shortness of breath (27%) or a high blood pressure (14%). On the Borg scale, 88% of the participants exerted themselves at least 'somewhat hard' and the participants achieved 91% of their age-predicted maximal heart rate. In 30% of the participants the ECG showed ST-shifts during the exercise test. After evaluation by the cardiologist (myocardium perfusion imaging in 30 participants and coronary angiography in 8 participants), significant CAD, requiring a change of medical treatment or an intervention, was diagnosed in an additional 7 participants.
## Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Baseline study sample (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64 (SD = 10)</td>
</tr>
<tr>
<td>Male</td>
<td>70 (62 %)</td>
</tr>
<tr>
<td><strong>Stroke characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Minor ischemic stroke</td>
<td>55 (49 %)</td>
</tr>
<tr>
<td>NIHSS(^a)</td>
<td>0 (0;3)</td>
</tr>
<tr>
<td>Lower extremity deficit</td>
<td>5 (4 %)</td>
</tr>
<tr>
<td>MMSE(^a)</td>
<td>29 (24;30)</td>
</tr>
<tr>
<td>Etiology(^b)</td>
<td></td>
</tr>
<tr>
<td>Lacunar syndrome</td>
<td>36 (32 %)</td>
</tr>
<tr>
<td>Stenosis &gt; 50 % of carotid or vertebral artery</td>
<td>13 (12 %)</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>2 (2 %)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>64 (57 %)</td>
</tr>
<tr>
<td><strong>History of disease</strong></td>
<td></td>
</tr>
<tr>
<td>Previous TIA or stroke</td>
<td>27 (24 %)</td>
</tr>
<tr>
<td>CAD</td>
<td>14 (12 %)</td>
</tr>
<tr>
<td>PAD or other vascular disease</td>
<td>5 (4 %)</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (5 %)</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>9 (8 %)</td>
</tr>
<tr>
<td>Beta-blocker medication</td>
<td>25 (22 %)</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension(^c)</td>
<td>87 (77 %)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (12 %)</td>
</tr>
<tr>
<td>Hyperlipidemia(^d)</td>
<td>95 (84 %)</td>
</tr>
<tr>
<td>Alcohol consumption (drinks per day)(^a)</td>
<td>0 (0–8)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>23 (20 %)</td>
</tr>
<tr>
<td>Pack-years(^a)</td>
<td>11 (0; 90)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>27.5 (SD = 4.0)</td>
</tr>
<tr>
<td>Physical activity (PASE)</td>
<td>126 (SD = 67)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentages) or mean (standard deviation).

\(^a\) Median (10; 90\(^{th}\) percentile)

\(^b\) Multiple etiologies are possible.

\(^c\) Hypertension was defined as blood pressure lowering drug use or blood pressure at baseline assessment > 140/90mmHg.

\(^d\) Hyperlipidemia was defined as low-density lipoprotein cholesterol 2.5 mmol L\(^{-1}\) or lipid lowering drug use at inclusion.

NIHSS indicates National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; PASE, Physical Activity Scale for the Elderly.
Table 2 Maximal exercise test

<table>
<thead>
<tr>
<th>Maximal exercise test</th>
<th>Baseline study sample (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak exercise capacity (ml/kg/min)</td>
<td>22.5 (SD = 6.4)</td>
</tr>
<tr>
<td>Peak power (Watt)</td>
<td>144 (SD = 55)</td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>137 (SD = 22)</td>
</tr>
<tr>
<td>Peak blood pressure (mmHg)</td>
<td>205/98</td>
</tr>
<tr>
<td>ST-shifts during exercise</td>
<td>34 (30%)</td>
</tr>
<tr>
<td>Reason to stop</td>
<td></td>
</tr>
<tr>
<td>Leg complaints</td>
<td>51 (41%)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>30 (27%)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>14 (12%)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentages) or mean (standard deviation).

Higher age and female sex were associated with a lower VO2peak; age per 10 years (B (95%CI); -2.57 (-3.75; -1.40)) and female sex (-5.84 (-8.06; -3.62)). In Table 3, the results of the age- and sex-adjusted linear regression analyses are shown. A history of cardiac disease, other vascular disease or COPD were associated with a lower VO2peak. A history of previous TIA or stroke was not associated with a lower VO2peak. The use of beta-blockers was associated with a lower VO2peak. Hypertension, BMI and smoking were also associated with a lower VO2peak, whereas more physical activity and higher alcohol consumption were associated with a higher VO2peak. The VO2peak was not different in patients with minor ischemic stroke compared with patients with a TIA. Neither the severity of the neurological deficit, the presence of lower extremity deficits nor the stroke etiology was associated with a significant change in VO2peak.

After exclusion of patients with a history of CAD, other vascular disease or COPD (n = 22), the associations between the VO2peak and pack-years, alcohol consumption and the use of beta-blockers were no longer significant (Table 4). The associations with physical activity and BMI remained significant and were borderline significant for hypertension.
Fitness after TIA and minor stroke

**Table 3** Determinants of peak exercise capacity

<table>
<thead>
<tr>
<th>Stroke characteristics</th>
<th>Difference in VO2peak B (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor ischemic stroke</td>
<td>-0.32 (-2.36; 1.72)</td>
<td>0.76</td>
</tr>
<tr>
<td>NIHSS</td>
<td>-0.09 (-1.40; 1.22)</td>
<td>0.89</td>
</tr>
<tr>
<td>Lower extremity deficit</td>
<td>-2.94 (-7.91; 2.03)</td>
<td>0.24</td>
</tr>
<tr>
<td>Lacunar syndrome</td>
<td>0.32 (-1.89; 2.54)</td>
<td>0.77</td>
</tr>
<tr>
<td>Stenosis &gt; 50% of carotid or vertebral artery</td>
<td>0.14 (-3.04; 3.33)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of disease</th>
<th>Difference in VO2peak B (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous TIA or stroke</td>
<td>-0.59 (-2.99; 1.80)</td>
<td>0.63</td>
</tr>
<tr>
<td>CAD</td>
<td>-4.12 (-7.22; -1.02)</td>
<td>0.01</td>
</tr>
<tr>
<td>PAD or other vascular disease</td>
<td>-7.04 (-11.81; -2.27)</td>
<td>0.004</td>
</tr>
<tr>
<td>COPD</td>
<td>-6.81 (-11.25; -2.37)</td>
<td>0.003</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>-2.95 (-6.68; 0.78)</td>
<td>0.12</td>
</tr>
<tr>
<td>Beta-blocker medication</td>
<td>-4.12 (-6.49; -1.76)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular risk factors</th>
<th>Difference in VO2peak B (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>-2.52 (-4.89; -0.15)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.87 (-1.96; 3.69)</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-2.95 (-5.98; 0.08)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pack-years</td>
<td>-0.07 (-0.13; -0.01)</td>
<td>0.02</td>
</tr>
<tr>
<td>Alcohol consumption (drinks per day)</td>
<td>0.99 (0.30; 1.68)</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.66 (-0.89; -0.43)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Physical activity (PASE)</td>
<td>0.03 (0.01; 0.04)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Age and sex-adjusted linear regression analysis.

NIHSS indicates National Institutes of Health Stroke Scale; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index, PASE, Physical Activity Scale for the Elderly.

**Table 4** Associations with peak exercise capacity after exclusion of patients with CAD, other vascular disease or COPD (n = 22)

<table>
<thead>
<tr>
<th>Vascular risk factors</th>
<th>Difference in VO2peak B (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker medication</td>
<td>-2.16 (-5.20; 0.88)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

| Hypertension                                  | -2.34 (-4.72; 0.04)              | 0.05    |
| Pack-years                                     | -0.04 (-0.11; 0.02)              | 0.21    |
| Alcohol consumption (drinks per day)          | 0.64 (-0.05; 1.33)               | 0.07    |
| BMI in kg/m²                                   | -0.82 (-1.04; -0.60)             | < 0.001 |
| Physical activity (PASE)                      | 0.02 (0.00; 0.03)                | 0.01    |

Age and sex-adjusted linear regression analysis.

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index, PASE, Physical Activity Scale for the Elderly.
DISCUSSION

In this study, the majority of patients with a recent TIA or minor ischemic stroke demonstrated a poor CRF. Apart from age and sex, important determinants for a low VO2peak were a history of CAD or other vascular disease, pulmonary disease and vascular risk factors such as overweight, physical inactivity and hypertension. History of previous TIA or stroke and stroke characteristics were not associated with the VO2peak.

Although the observed CRF in our study was higher than previously reported in patients with disabling stroke, it was still poor in the majority of patients. Half of the patients attained a value less than the 5th percentile of age and sex and 12% had a value less than 15ml/kg/min, which is necessary to meet the physiological demands for independent living. In addition, only 5% of patients achieved an exercise capacity corresponding to a fair fitness category according to the ACSM guidelines. This CRF is similar to the value found in our pilot study and slightly lower than the value of 25 ml/kg/minute observed in another study with 88 patients with TIA or minor stroke. Our observed percentage of the predicted maximal heart rate was higher than in other studies in patients with a recent disabling stroke, suggesting a substantial level of physical exertion.

To our knowledge, this is the first study that examined the CRF and its possible determinants in patients with a recent TIA or a minor ischemic stroke. In general, CRF is dependent on the integrated physiological and functional state of the respiratory, cardiovascular and musculoskeletal systems. The CRF can be influenced by neurological deficit, limiting the use of the musculoskeletal systems, and by cardiac and pulmonary disease. Interestingly, the diagnosis of minor ischemic stroke versus TIA at inclusion and a history of previous TIA or stroke were not associated with a change in CRF in this study. In addition, contrary to other studies in patients with disabling stroke, the severity of the neurological deficit was not associated with CRF. A probable explanation is the absence of severe neurological deficits in our patients. These findings suggest that the low CRF found in our group of patients with TIA or a minor stroke was not caused by TIA- or stroke-related factors, but that other factors such as underlying cardiopulmonary disease may be more important determinants.

CAD, other vascular disease such as PAD and COPD were indeed associated with a lower CRF. The association with CAD has been described before and can be explained by a reduced capacity to increase cardiac output in response to exercise. The association of CRF with COPD and PAD and other vascular disease has not been described before in stroke patients, but can be explained by an early dyspnea or fatigue in patients with COPD and an impairment of muscle O2-supply in patients with PAD.

As expected, higher age and female sex had a negative influence on CRF. The 11% decrease per decade and the finding that VO2peak values for women are approximately 75% of that for men, is comparable to the general population. There is considerable evidence that the physical activity level influences CRF, but this association is also modified.
by age and possibly also by genetic factors. In our study, patients with a higher level of physical activity also demonstrated a higher CRF.

Higher BMI and hypertension were associated with a lower CRF, also after exclusion of patients with history of vascular disease or COPD. Earlier studies in patients with stroke did not find such associations. Obesity can lead to higher metabolic requirements during exercise and respiratory restriction and therefore a lower CRF. In patients with PAD, BMI was also associated with a lower CRF, but a recent study reported that the lean tissue mass of the legs, a marker of muscle mass, was the most important factor associated with the CRF. High blood pressure was a reason to terminate the exercise test in 14%; this could be an explanation for the found relation with hypertension.

Twelve percent of the participants had a history of CAD and we found significant CAD in an additional 6% of patients, resulting in a prevalence of CAD in 18% of our study population. This finding confirms previous studies reporting a high prevalence of CAD. Therefore, patients with a TIA or minor stroke should be regarded as a high-risk population and before advocating an exercise program in the context of rehabilitation, physicians should consider the need of a supervised exercise test.

Twelve percent of the participants had a history of CAD and we found significant CAD in an additional 6% of patients, resulting in a prevalence of CAD in 18% of our study population. This finding confirms previous studies reporting a high prevalence of CAD. Therefore, patients with a TIA or minor stroke should be regarded as a high-risk population and before advocating an exercise program in the context of rehabilitation, physicians should consider the need of a supervised exercise test.

Strengths of our study are the relatively large sample of patients with TIA and minor stroke with a measurement of the CRF using the gold standard and the systematically and nearly complete information obtained. A limitation is the measurement of VO2peak on a cycle ergometer. The CRF can be measured using a treadmill, cycle ergometer or arm ergometer for patients who cannot perform leg exercise, or can be estimated using submaximal tests. Cycle ergometers have advantages over treadmill, as it is easier to obtain ECG recordings and blood pressure measurements, which is important in patients with cardiovascular disease. However, the results of our study cannot be directly compared with normative values, because these normative values are derived from treadmill examinations. The VO2peak is approximately 10% higher on the treadmill than on the cycle ergometer, but this difference can be larger in populations with an unfamiliarity with cycling. Unfamiliarity of patients with cycling is generally not a problem in the Dutch population and therefore the difference with treadmill-derived normative values will be no more than 10%. Indeed the fitness level was still very poor in the majority of patients after a 10% correction of these normative values. Finally, it is not clear whether the results of the present study can be generalized because patients were recruited from a single institution and we included a relatively low percentage of patients with a cardioembolic etiology.

In conclusion, the majority of patients with a recent TIA or a minor ischemic stroke have a poor CRF. Our findings suggest that in this group of patients the poor CRF is not explained by TIA- or stroke-related factors, but apart from age and sex by premorbid cardiopulmonary disease and vascular risk factors. We recommend that physical exercise programs should not only be investigated in patients with disabling stroke, but also in patients with TIA or minor stroke.
REFERENCES


Fitness after TIA and minor stroke


