CHAPTER 6

Safety and feasibility of post-stroke care and exercise after minor ischemic stroke or transient ischemic attack: MotiveS & MoveIT

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A B S T R A C T

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.[6,12] 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 randomised 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

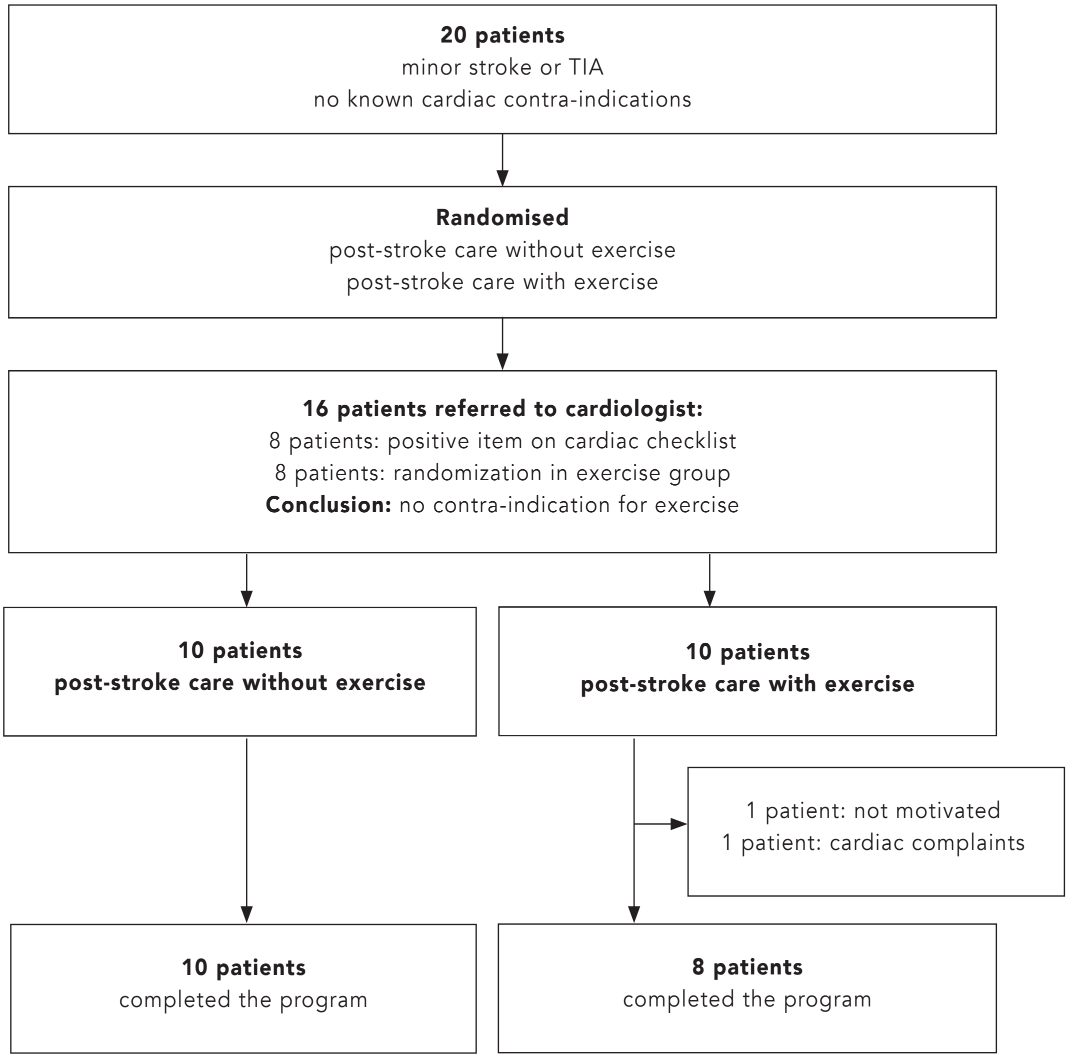
Study design

We conducted a prospective, single-blinded, randomised 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.

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 ≤3[16] **(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

FIGURE 1 **Flowchart summarizing the progress of the pilot study**



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.[17] Exercise was terminated if patients were fatigued or earlier when fulfilling the ACSM's guidelines 'Indications for terminating Exercise Testing'.[17] 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 mm Hg) and LDL-C (<100 mg/dl) targets. These cut-off points were based on current guidelines.[3] Other endpoints were the individual components of the composite endpoint of optimal medical therapy, medication adherence (Morisky medication adherence scale)[18], 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-squared 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.

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

TABLE 1 **Baseline characteristics**

	Post-stroke care without exercise	Post-stroke care with exercise
Patients (n)	10	10
Male (n)	7	7
Age (mean, range)	63.0 (46-78)	62.4 (46-73)
Stroke (n)	7	5
TIA (n)	3	5
NIHSS (median, range)	1 (0-3)	0 (0-2)
Vascular risk factors		
AF (n)	0	1
Hypertension (n)	6	7
Blood pressure (mean)	161/84 mm Hg	155/82 mm Hg
LDL-C (mean)	127.6 mg/dl	123.7 mg/dl
Diabetes mellitus (n)	2	1
History of CVD (n)	4	2
History of stroke (n)	3	2
MMSE (median, range)	29.5(28-30)	28.5 (24-30)
VO2max (median, range)	20.8 (12.9-30.1)	22.9 (11.9-45.4)

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 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 22 ml/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).

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.

Discussion

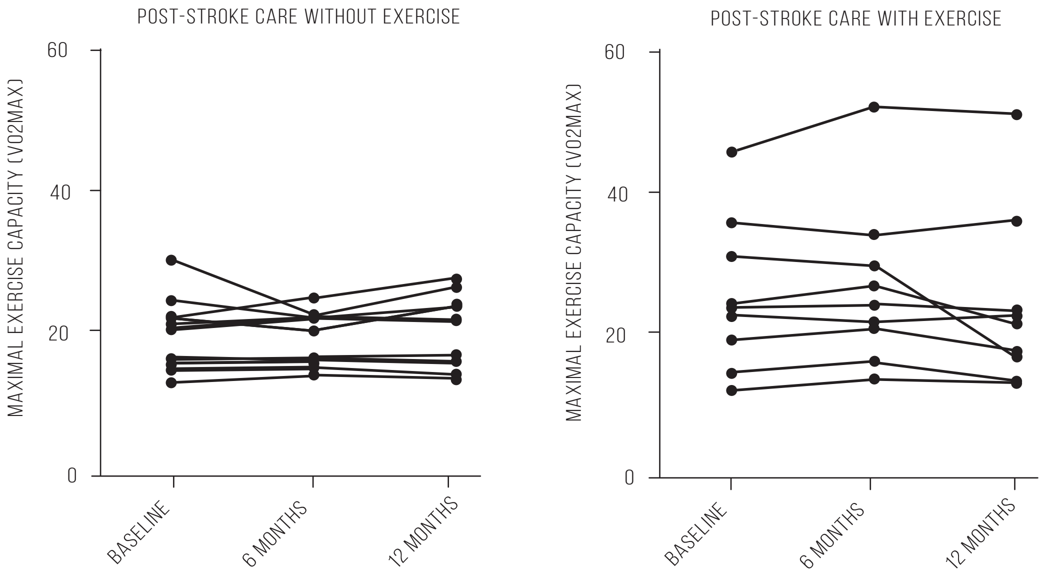
In this pilot study we have demonstrated that in the acute phase after a minor ischemic stroke or TIA post- stroke care including an exercise program, similar to cardiac rehabilitation, is safe and feasible. Improving adherence to guidelines and lifestyle changes by such a program might be a way to increase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

TABLE 2 Secondary prevention targets after 12 months

	Post-stroke care without exercise	Post-stroke care with exercise	p-value
Patients (n)	10	10	
Optimal therapy (n)	2	7*	0.038
Use of antithrombotics (n)	10	10	NS
Blood pressure ≤140/90 mm Hg (n)	8	9	NS
Blood pressure (mean)	127/75 mm Hg	120/71 mm Hg	NS
LDL-C ≤100 mg/dl (n)	3	8*	0.037
LDL-C (mean)	98.6 mg/dl	82.0 mg/dl	NS

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

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.

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 randomised 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.[13,14] 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.[19] 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.[13,14,19] Apart from our pilot study, only one small, randomised 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.[15]

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.[20] In addition, the low median VO2 max in our patients was close to the 21ml/kg/min level, which in previous studies has been associated with an increased mortality among patients with coronary artery disease.[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.[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.[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.[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.[24] However, it remains uncertain whether there is a causal relation between physical exercise and cholesterol levels. Further randomised 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.

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