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ORIGINAL RESEARCH

Effects of High-Intensity Interval Training After Stroke (the HIIT-Stroke Study): A Multicenter Randomized Controlled Trial

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Abstract

Objective: To examine if 8 weeks of high-intensity interval training (HIIT) in addition to standard care would increase and maintain peak oxygen uptake (Vo_{2peak}) more than standard care alone in patients with stroke.

Design: This was a single-blind, multicenter, parallel group, randomized controlled trial.

Setting: Specialized rehabilitation units at 3 Norwegian hospitals.

Participants: Participants (N=70), 3 months to 5 years after first-ever stroke, were randomly assigned to the intervention group (n=36) or the control group (n=34); 42% were women, mean age was 57.6±9.3 years, mean time post stroke was 26.4±14.5 months.

Intervention: The intervention was 8 weeks: 3 times a week with HIIT treadmill training with work periods of 4 × 4 minutes at 85%-95% of peak heart rate interspersed with 3 minutes of active recovery at 50%-70% of peak heart rate. The control group received standard care according to national guidelines.

Outcomes: The primary outcome, analyzed by intention-to-treat, was Vo_{2peak} measured as liters per minute 12 months after inclusion. Secondary outcome measures were blood pressure and blood profile.

Results: Mean baseline Vo_{2peak} was 2.63±1.08 $L \cdot min^{-1}$ vs 2.87±0.71 $L \cdot min^{-1}$, while at 12 months Vo_{2peak} was 2.70±1.00 $L \cdot min^{-1}$ vs 2.67±0.76 $L \cdot min^{-1}$ (P=.068) in the intervention and control groups, respectively. There was a significant and greater improvement in the intervention group compared with the control group at 12 months in 3 of 6 secondary outcomes from the peak test but no significant differences for blood pressure or blood profile.

Conclusions: The HIIT intervention, which was well-tolerated in this sample of well-functioning survivors of stroke, was not superior to standard care in improving and maintaining Vo_{2peak} at the 12-month follow-up. However, secondary results from the peak test showed a significant improvement from before to immediately after the intervention.

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In the general population, substantial evidence from large epidemiologic studies suggest that high levels of physical activity and exercise are beneficial for mitigating modifiable risk factors, such as hypertension and dyslipidemia. After a stroke, it is recommended that routine activities should be supplemented by moderate physical exercise for 30-60 minutes 4-7 days per week to reduce the risk of recurrent stroke.[1,2] However, exercise training as a model to reduce the risk of a second stroke is poorly investigated,[3] and the evidence for these recommendations is based mainly on expert opinion and extrapolated results from studies in primary prevention.[4] Despite the recommended activity levels, the majority of survivors of stroke are inactive, have low aerobic capacity, and experience increased effort during activities of daily living, thus making it hard for them to comply with the recommendations.[5-7]

Peak oxygen uptake (Vo_{2peak}) is shown to be a strong and independent risk factor for cardiovascular health and premature mortality.[8,9] A recent review highlights the importance of finding the optimal training mode and intensity to improve Vo_{2peak} in the population with stroke.[10]

High-intensity interval training (HIIT) is based on high-intensity aerobic exercise training sessions at intensities close to Vo_{2peak} that are interspersed with work periods at lower intensities that allow recovery.[11] HIIT with an intervention period of 4 weeks or more has been shown to increase Vo_{2peak} more than continuous moderate intensity training in patients with heart disease and in the healthy population.[12-14] There is strong evidence that cardiorespiratory fitness training can improve exercise and walking ability after a stroke.[6] To date, only a few studies have examined HIIT in the population with stroke showing that the intervention is feasible and providing promising findings for both Vo_{2peak} and function.[15-17] However, high-quality randomized controlled trials, with a long-term follow-up period and aiming to examine the efficacy of HIIT in the prevention of a second stroke, are needed.[10]

The primary aim of this study was to investigate if an 8-week treadmill training program with supervised and individually tailored HIIT in addition to standard care was superior to standard care alone for increasing and maintaining a high Vo_{2peak} in a sample of survivors of subacute and chronic stroke. The secondary aim was to investigate the effects of HIIT on blood pressure and blood profiles. Our primary hypothesis was that an 8-week HIIT program would be superior to standard care with respect to Vo_{2peak} at the 12-month follow-up.

Methods

Study design, setting, and participants

This was a single-blind, multicenter, randomized controlled trial performed in collaboration with specialized rehabilitation units at 3 hospitals in Norway. Eligible participants were recruited from patient lists at each hospital and were contacted with information about the study from the study coordinator at each hospital. Inclusion started in September 2015, and data collection ended in December 2017. Groups of 10-22 participants were included at a time.

Inclusion criteria were first-ever stroke (ischemic or hemorrhagic) verified with computed tomography and/or magnetic resonance imaging, willing and able to give informed consent, independent walking with or without an assistive device, minimum of 3 months and maximum of 5 years post stroke, living in the community and able to travel to the assessment and training site, approval to participate from the study's responsible medical physician and a score on the modified Rankin Scale of 0-3. Exclusion criteria were instability of cardiac conditions (eg, serious rhythm disorder or valve malfunction), poorly controlled hypertension (>180/100) measured at rest, any other medical condition where the test of Vo_{2peak} was contraindicated, subarachnoid hemorrhage, or participation in another ongoing intervention study.

The HIIT-Stroke Study was conducted in accordance with the institutional guidelines at each participating hospital and was approved by the Regional Committee of Medical and Health Research Ethics (REC no. 2015/563).

List of abbreviations:

HIIT	**high-intensity interval training**
PT	**physical therapist**
Vo_{2peak}	**peak oxygen uptake**

Intervention and control

Standard care

Participants assigned to the control group received standard care. The Norwegian guidelines recommend patients with chronic stroke be physically active and engage in activities with moderate to high intensity 3-5 days per week. All participants received information about the importance of high levels of physical activity and exercise training after a stroke in the baseline testing.

High-intensity interval training

In addition to standard care, the participants in the intervention group received HIIT. The training protocol was repeated 3 times per week for 8 consecutive weeks, giving a total of 24 training sessions. Two participants trained at the same time on treadmills controlled by 1 experienced physical therapist (PT). Each training session started with a 10-minute warm-up period when the treadmill speed and/or inclination was gradually increased to reach target training intensity. After the initial warm-up period, the HIIT protocol compromised 4-minute intervals (4 × 4) at 85%-95% of peak heart rate interspersed with 3 minutes of active breaks at 50%-70% of peak heart rate. Total exercise time was 38 minutes. The exercise intensity was set based on the peak heart rate from the Vo_{2peak} test controlled with heart rate monitors (Polar A300).[a] The Borg rating of perceived exertion scale was recorded at the end of each high-intensity period.

A priori, we set a completion of 18 of the 24 training sessions as successfully adhering to the training protocol. If less than 2 high-intensity periods were completed, the training session was not considered to have been completed successfully.

After 8 weeks of HIIT the participants were invited 3 times to the training facility in groups of 5-11 participants to encourage them to maintain their physical activity levels. The meetings were led by the person who administered the HIIT at each hospital.

Outcomes

Participants were assessed at 3 time points: (1) at baseline, approximately 1 week before initiating the intervention, (2) at post

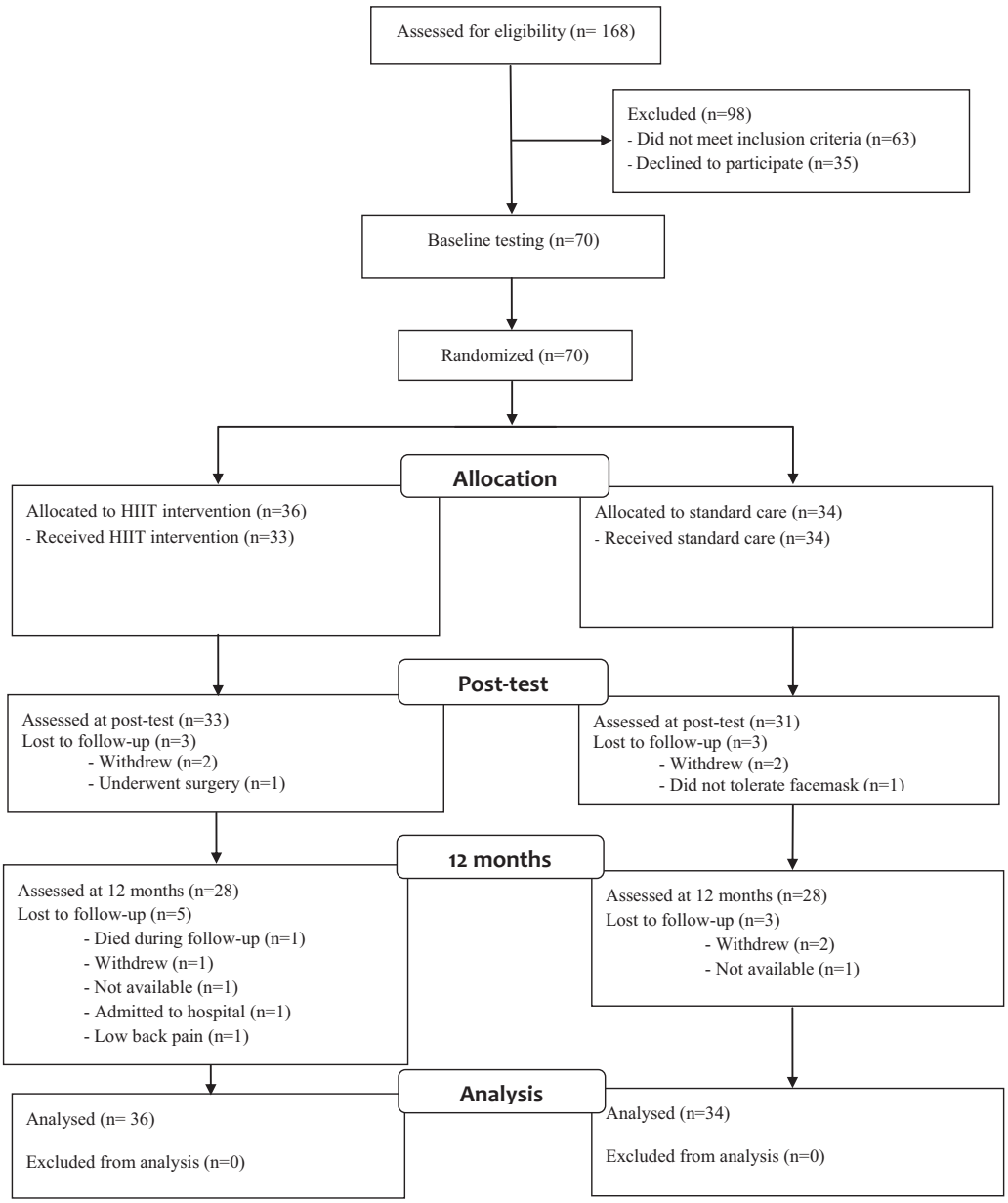

Fig 1 Study enrollment, randomization, and follow-up.

test, within 1 week after the 8-week intervention period, and (3) at follow-up, 12 months after inclusion. All tests were completed (peak test, blood pressure measurements, and blood tests) within 1 week at each time point.

The primary outcome measure was Vo_{2peak} measured in liters per minute, assessed with a graded exercise treadmill test[b,c] 12 months after inclusion. Secondary outcomes were Vo_{2peak} measured as milliliters per kilogram, systolic and diastolic blood pressures measured on the nonaffected arm at rest, and blood profiles (ie, lipid levels and insulin resistance) measured both at post test and at 12 months. Heart rate, lactate, minute ventilation, respiratory exchange ratio, Borg scale, and carbon dioxide output were obtained to ensure adherence to the peak test protocol. All tests were performed by experienced PTs blinded to group assignment and previous test results.

For the Vo_{2peak} measurements, the MetaMax II portable ergospirometry system[b] and software were used at all test sites and time points. Calibration was performed according to the manufacturer's procedures. The equipment had previously been validated for ventilatory and metabolic demand in a healthy population.[18] To assess Vo_{2peak}, a cardiopulmonary exercise treadmill test[d] with an individual ramp protocol was used. After a 10-15−minute warm-up period, the speed was increased by 0.5-1.0 km/h^{-1} or the inclination was increased by 1%-2%, while the participant maintained a stable oxygen uptake for >30 seconds. Vo_{2peak} was defined as the average of the 3 highest oxygen uptake measurements obtained during the incremental treadmill test. Reasons for terminating the test were subjective exhaustion or standard clinical criteria.[19] Peak heart rate was the highest registered heart rate during the Vo_{2peak} test.

Table 1 Characteristics of participants at inclusion

Variables	Intervention (n=36)	Control (n=34)
Age (y)		
Mean ± SD	57.6±9.2	58.7±9.2
Range	41-71	34-72
Male, n (%)	21 (58.3)	20 (58.8)
Time since stroke (mo), mean ± SD	25.4±14.5	27.4±14.7
Crutch, n (%)	4 (11.1)	2 (5.9)
Hypertension, n (%)	20 (54.1)	17 (44.9)
Beta blocker, n (%)	6 (16.7)	0 (0.0)
Affected side, n (%)		
Right	15 (41.7)	10 (29.4)
Left	15 (41.7)	19 (55.9)
Both	6 (16.7)	5 (14.7)
Stroke type, n (%)		
Infarct	29 (80.6)	28 (82.4)
Hemorrhage	7 (19.4)	6 (17.6)
mRS (0-5), mean ±SD	1.8±0.8	1.77±0.7
mRS 0, n (%)	2 (5.6)	1 (2.9)
mRS 1, n (%)	10 (27.8)	10 (29.4)
mRS 2, n (%)	17 (47.2)	16 (47.1)
mRS 3, n (%)	7 (19.4)	7 (20.6)
Height (cm), mean ± SD	174.2±10.4	176.81±7.9
Weight (kg), mean ± SD	82.1±15.6	87.47±18.6
BMI, mean ± SD	26.86±3.71	27.78±4.77
10-m preferred walking speed (m/s), mean ± SD	1.4±0.4	1.3±0.4
Bergs balance scale (0-56), mean ± SD	53.0±5.7	54.0±2.7

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); mRS, modified Rankin Scale.

Blood pressure was measured according to recommended procedures[20] with an automated device[c] before the Vo_{2peak} test and after a 5-minute seated rest period.[20] The mean of 3 consecutive measurements with an interval of 1 minute between the measurements was used in data analysis.

Blood tests were taken on a separate day from the graded treadmill test after a 12-hour fast. The following blood tests were taken: hemoglobin, low-density lipoprotein, high-density lipoprotein, total cholesterol, triglycerides, glycosylated hemoglobin, and C-peptide. All blood tests were analyzed by the laboratory at each hospital according to standard procedures.

Compliance

Adherence to the HIIT-protocol was obtained by measuring heart rate and rating on the Borg scale during the high-intensity periods.

Adherence to the recommended habitual daily activity was measured in both groups by a single sensor, activPAL,[e] attached to the participant's nonaffected thigh for 7 consecutive days immediately after baseline testing, post test, and follow-up. The activPAL has been validated in the population with stroke.[21]

Safety

Information about new cerebrovascular or cardiovascular events was gathered from the participant's hospital record and from the patient or next of kin. Hospitalization, serious falls, fractures, and syncope were also classified as serious adverse events.

Randomization

Randomization was performed by a web-based randomization system with blocks of various sizes, stratified by hospital site, and administered by the Unit for Applied Clinical Research, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim.

Sample size and statistical methods

Based on data from 2 previous pilot studies,[15,16] we estimated a mean Vo_{2peak} to be 2.27±0.45 $L \cdot min^{-1}$ at inclusion. Because most intervention studies also report positive responses in the control group, we estimated a minimal improvement of 2% after the 8-week intervention period to 2.32±0.44 $L \cdot min^{-1}$ and a 10% increase in Vo_{2peak} in the intervention group to 2.6±0.55 $L \cdot min^{-1}$, which continued to 12-month follow-up. Based on these assumptions, we estimated that 32 participants in each group needed to reach a power of 80% with a P value of .05. We expected a 10% dropout, so the total number of participants was set to 70.

Mixed models were used to evaluate differences between the groups for the primary and secondary end points. As recommended by Twisk et al,[22] we adjusted for baseline difference for the outcome of interest. We included indicator variables for the posttest and follow-up time points and their interactions with the treatment group and hospital as fixed factors. In this model, the coefficients for the interaction terms give the estimated treatment effects at post test and follow-up. This corresponds to equation (2d) in Twisk et al.[22]

Adherence to the intervention was estimated by calculating the mean ± SD percentage of heart rate during the final 2 minutes of the last interval in each training session. In addition, the mean ± SD rating on the Borg scale immediately after the fourth interval was recorded. Adherence to leisure time physical activity was estimated based on the mean ± SD of 4 consecutive 24-hour recordings from activPAL. The day of attachment of the activPAL was excluded from the analysis. IBM SPSS Statistics version 25[f] was used for all statistical analyses.

Results

We screened a total of 168 patients from the patient lists at the 3 collaborating hospitals. Seventy consenting participants with first-ever stroke were included and randomly assigned to either the intervention group (n=36) or the control group (n=34). Two participants sent to the intervention group withdrew from the study after the first week of training, and 1 discontinued because of a prescheduled surgery not related to the intervention protocol (fig 1).

The mean age was 57.6±9.2 years in the intervention group and 58.7±9.2 years in the control group. Twenty-nine participants (80.5%) in the intervention group and 27 (79.5%) in the control group had a modified Rankin Scale score≤2 (table 1).

For the primary outcome, the mean baseline Vo_{2peak} was 2.63±1.08 $L \cdot min^{-1}$ vs 2.87±0.71 $L \cdot min^{-1}$, while at follow-up Vo_{2peak} was 2.70±1.03 $L \cdot min^{-1}$ vs 2.67±0.76 $L \cdot min^{-1}$ (P=.657) in the intervention group and the control group, respectively (table 2 and fig 2).

Table 2 Primary and secondary outcome measures at baseline, post test, and follow-up and estimated treatment effect (coefficient for the interaction term) from the mixed-model analyses

	Intervention (n=36)			Control (n=34)			Difference (Group × Time)		
Variables	n	Mean	SD	n	Mean	SD	Estimate	95% CI	*P* Value
Peak test									
$\dot{V}O_2$ (L/min^{-1})									
Baseline	36	2.63	1.08	34	2.87	0.71			
Post test	33	2.90	1.03	31	2.79	0.70	0.21	0.05-0.36	.009
Follow-up	28	2.70	1.00	28	2.67	0.76	0.15	−0.01 to 0.32	.068
$\dot{V}O_2$ (mL/kg/min^{-1})									
Baseline	36	31.83	11.18	34	33.35	8.85			
Post test	33	34.88	10.56	31	31.76	6.85	2.79	−4.48 to −1.10	.001
Follow-up	28	33.10	10.21	28	30.91	8.03	1.87	−3.65 to −0.66	.008
HR (beats/min^{-1})									
Baseline	36	160.39	22.53	34	164.15	10.37			
Post test	33	161.48	17.36	31	164.56	11.14	−0.33	−5.06 to 4.41	.892
Follow-up	28	163.04	18.17	28	163.29	15.23	−4.37	−9.40 to 0.66	.088
VE (L/min^{-1})									
Baseline	36	85.21	31.32	34	94.23	23.04			
Post test	33	93.84	27.14	31	90.69	25.12	−7.87	−13.64 to −2.11	.008
Follow-up	28	89.40	26.95	28	91.04	28.39	−6.98	−13.06 to −0.91	.025
Lactate (mmol/L)									
Baseline	36	8.36	3.23	33	8.02	2.67			
Post test	31	9.24	3.29	31	8.03	2.11	1.20	−2.26 to −0.15	.026
Follow-up	28	9.75	3.25	26	8.87	3.18	1.07	−2.18 to 0.05	.075
RER									
Baseline	36	1.06	0.08	34	1.06	0.07			
Post test	33	1.07	0.08	31	1.05	0.07	−0.03	−0.06 to 0.01	.112
Follow-up	28	1.07	0.09	28	1.06	0.10	−0.03	−0.06 to 0.00	.075
Borg (6-20)									
Baseline	36	16.78	1.48	34	16.62	1.76			
Post test	33	17.73	1.26	31	17.03	1.45	−0.56	−1.23 to 0.11	.100
Follow-up	28	17.20	1.37	28	16.57	1.87	−0.61	−1.33 to 0.11	.016
$\dot{V}CO_2$ (L/min^{-1})									
Baseline	36	2.82	1.17	34	3.05	0.76			
Post test	33	3.07	1.07	31	2.93	0.83	−0.22	−0.43 to −0.02	.035
Follow-up	28	2.90	1.07	28	2.78	0.95	−0.27	−0.04 to −0.05	.016
Blood pressure									
Systolic (mmHg)									
Baseline	35	138.46	16.00	34	141.00	13.94			
Post test	33	135.70	13.62	31	138.16	14.60	1.53	−4.88 to 7.94	.639
Follow-up	28	135.90	14.39	27	136.11	17.06	2.32	−4.59 to 9.23	.509
Diastolic (mmHg)									
Baseline	35	83.14	11.58	34	87.15	8.34			
Post test	33	83.42	7.35	31	86.59	9.73	1.56	−2.79 to 5.90	.481
Follow-up	28	82.93	7.39	27	85.70	10.40	1.72	−2.99 to 6.42	.472
Blood profiles									
Hb									
Baseline	33	14.37	1.23	34	14.61	1.22			
Post test	33	14.49	1.20	29	14.36	1.27	−0.17	−0.02 to 0.54	.346
Follow-up	22	14.34	1.09	25	14.54	1.41	−0.09	−0.32 to 0.50	.660
Cholesterol									
Baseline	33	4.30	1.06	34	4.52	1.28			
Post test	33	4.12	0.96	29	4.58	0.94	0.06	−0.26 to 0.34	.726
Follow-up	23	4.24	1.00	26	4.65	0.90	0.03	−0.31 to 0.38	.849
LDL									
Baseline	33	2.51	0.93	34	2.74	1.05			
Post test	33	2.31	0.88	29	2.70	0.93	0.06	−0.19 to 0.31	.642
Follow-up	23	2.41	0.92	26	2.79	0.87	−0.04	−0.31 to 0.23	.751

(*continued on next page*)

Table 2 (*continued*)

Variables	Intervention (n=36)			Control (n=34)			Difference (Group × Time)		
	n	Mean	SD	n	Mean	SD	Estimate	95% CI	*P* Value
HDL									
Baseline	33	1.43	0.44	34	1.49	0.48			
Post test	33	1.44	0.44	29	1.51	0.47	0.28	−0.14 to 0.09	.625
Follow-up	23	1.39	0.39	26	1.49	0.42	−0.12	−0.00 to 0.25	.060
Triglycerides									
Baseline	33	1.32	0.63	34	1.45	1.45			
Post test	33	1.24	0.53	29	1.51	1.63	0.14	−0.28 to 0.56	.506
Follow-up	22	1.49	0.75	26	1.24	0.52	−0.41	−0.87 to 0.06	.089
HbA1c									
Baseline	33	5.53	0.40	33	5.59	0.67			
Post test	33	5.54	0.41	26	5.57	0.67	−0.01	−0.25 to 0.27	.956
Follow-up	22	5.62	0.51	26	5.48	1.30	0.20	−0.49 to 0.09	.168
C-peptide									
Baseline	33	1155.79	755.48	32	1112.91	735.68			
Post test	27	1085.93	539.89	22	922.73	539.89	142.56	−468.02 to 182.89	.388
Follow-up	22	958.36	453.18	25	873.30	455.85	78.96	−409.70 to 251.78	.638

NOTE. The difference estimates are results from the baseline-adjusted linear mixed models (positive values favor intervention group). Post- = postintervention assessment. Follow-up = 12 months follow-up assessment (12 months after randomization).
Abbreviations: CO_2, carbon dioxide output; Hb, hemoglobin; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; RER, respiratory exchange ratio; VE, minute ventilation.

Of 792 planned training sessions, a total of 728 sessions were successfully completed (92%). Mean percentage of peak heart rate ranged from 90.0%±4.6% to 93.8%±3.8%. Mean ratings of perceived exertion on the Borg scale ranged from 15.5±1.9 to 16.6±1.5 (table 3).

The results from the activPAL showed no significant differences in habitual physical activity at baseline or during follow-up in both intervention and control groups (table 4).

There were 4 adverse events during follow-up in the intervention group, with 1 death, 1 upper limb fracture after a fall, 1 concussion, and 1 hospitalization because of femoral drainage. There were also 4 adverse events in the control group, with 1 transient ischemic attack, 1 aortic aneurism, 1 minor hemorrhage, and 1 epilepsy seizure.

Discussion

This is the first randomized controlled multicenter trial assessing the effect of HIIT on Vo_{2peak} in a population with stroke. The results showed that 24 sessions of treadmill HIIT for 8 weeks was superior to standard care alone to achieve a higher Vo_{2peak} ($L \cdot min^{-1}$) immediately after the intervention. However, the

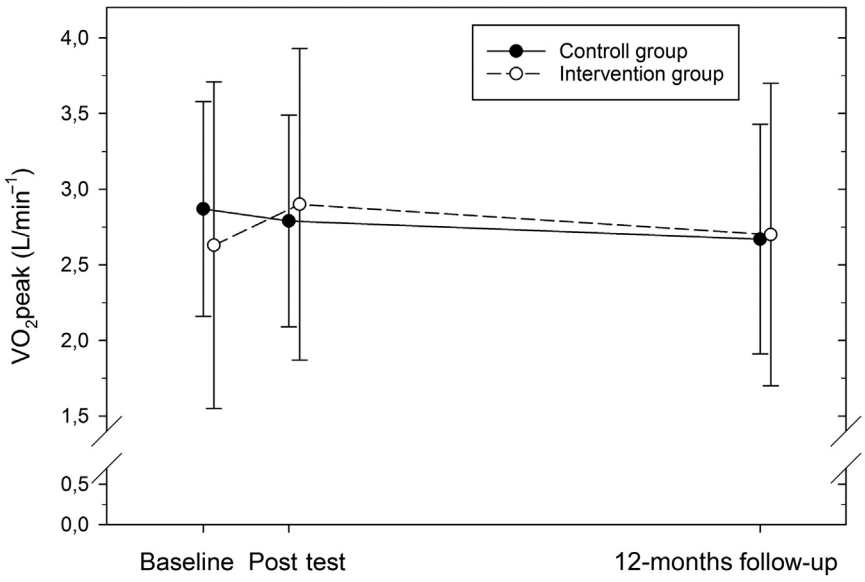

Fig 2 Mean VO_{peak} in $L \cdot min^{-1}$ at baseline, post test, and follow-up. Error bars represent SD.

Table 3 Exercise intensity presented as percentage of peak heart rate during the last 2 minutes of the 4th interval and rating of perceived exertion on the Borg's scale (6-20) at the end of the 4th interval, both registered in each training session

Training Session	1 (n=32)	2 (n=30)	3 (n=31)	4 (n=30)	5 (n=31)	6 (n=30)	7 (n=30)	8 (n=30)
% of peak HR, mean ± SD	90.0±4.6	91.3±4.5	91.7±3.6	91.8±2.7	92.1±3.8	92.0±3.73.7)	92.5±2.8	92.7±4.5
Borg scale, mean ± SD	15.5±1.9	16.1±1.2	16.3±1.7	16.1±1.7	16.3±1.7	16.2±1.3	16.3±1.4	16.3±1.3
Training Session	9 (n=32)	10 (n=32)	11 (n=32)	12 (n=31)	13 (n=28)	14 (n=31)	15 (n=31)	16 (n=31)
% of peak HR, mean ± SD	92.5±3.6	92.6±3.3	91.4±5.5	91.9±3.4	92.6±3.6	93.8±3.8	92.9±3.3	93.2±3.2
Borg scale, mean ± SD	16.1±1.5	16.3±1.4	16.4±1.4	16.1±1.3	16.0±1.5	16.3±1.3	16.2±1.3	16.1±1.1
Training Session	17 (n=29)	18 (n=30)	19 (n=33)	20 (n=29)	21 (n=31)	22 (n=32)	23 (n=31)	24 (n=26)
% of peak HR, mean ± SD	92.3±3.6	92.5±5.0	92.4±3.8	92.4±3.8	92.6±3.2	92.6±4.8	93.6±4.4	93.6±5.8
Borg scale, mean ± SD	16.1±1.8	15.8±1.5	16.2±1.4	16.3±1.3	16.3±1.7	16.1±1.4	16.3±1.4	16.6±1.5

Abbreviation: HR, heart rate.

difference between the groups was not maintained at the 12-month follow-up.

As shown in fig 2, the intervention and control group revealed different trajectories during follow-up, with a significantly greater improvement in the intervention group at post test followed by a corresponding decline until the end of follow-up, giving neutral results at 12 months. Nevertheless, the improvement shown within the intervention group was in line with findings from studies with the same 4 × 4 HIIT protocols in cardiac patients and in healthy individuals.[12,13,23] Hence, our results give important directions for future research, and this trial needs to be replicated before a final conclusion can be reached.

One key component to successful HIIT is the training intensity during periods with intensities between 85%-95% of peak heart rate.[11] We ensured the intensity by having experienced PTs adjusting the treadmill speed and inclination to be within the prespecified heart rate intensity zone. This contrasts with previous research in the population with stroke where the intensity is set by treadmill speed and walking function rather than the physiological stress on the system.[17]

The activPAL data showed that the intervention group failed to achieve and maintain a higher habitual daily activity level compared with the control group, which might explain the slight decrease in Vo_{2peak} in both groups from post test to 12 months.

One participant in the intervention group died before the 12-month follow-up. Investigations from the medical physician concluded that there was no association between the cause of death and participation in this study. The intervention and test protocol seem safe and were well tolerated among all participants as shown by the adherence rate of 92%. No injuries were reported during testing or treadmill training. This is in line with comparable studies applying the same intervention in various groups of patients in the healthy population[23-25] and in studies conducted so far in the population with stroke.[15,16]

A major strength of the present study was it being a high-quality multicenter trial with randomization of participants and blinded outcome assessment. The mixed-model statistical analyses have 2 advantages compared with methods based on complete cases. First, complete case analysis is unbiased only if data are missing completely at random, while a linear mixed model gives

Table 4 Leisure time physical activity data at baseline, post test, and follow-up

	Intervention			Control			
Baseline	n	Mean	SD	n	Mean	SD	*P* Value
Time sitting/lying, h/24h	32	18.94	1.06	29	19.09	1.50	.64
Standing time, h/24h	32	3.42	0.80	29	3.11	1.03	.82
Stepping time, h/24h	32	1.64	0.60	29	1.80	0.67	.33
Step count, number/24h	32	7321.6	3517.1	29	8481.4	3445.1	.20
Transitions, number/24h	32	54.84	19.92	29	54.25	15.53	.90
Post test							
Time sitting/lying, h/24h	31	18.89	1.58	27	18.66	1.86	.61
Standing time, h/24h	31	3.55	1.08	27	3.48	1.35	.82
Stepping time, h/24h	31	1.55	0.69	27	1.86	0.71	.10
Step count, number/24h	31	6903.5	3311.6	27	8621.0	3672.7	.07
Transitions, number/24h	31	52.10	15.54	27	54.01	16.24	.65
Follow-up							
Time sitting/lying, h/24h	27	18.48	1.94	28	19.20	1.65	.14
Standing time, h/24h	27	3.89	1.38	28	3.01	1.10	.01
Stepping time, h/24h	27	1.63	0.77	28	1.79	0.71	.42
Step count, number/24h	27	6835.7	3774.7	28	8334.7	3817.3	.15
Transitions, number/24h	27	47.58	12.66	28	50.63	15.01	.42

unbiased estimates also under the less restrictive missing-at-random assumption. Second, a mixed model uses data from all participants, including those with partially missing data, avoiding unnecessary loss of statistical power. Third, this method allows for adjustment of baseline values as recommended by Twisk et al.[22] Another strength was the very good compliance to the training protocol and interval sessions by the participants in the intervention group. Each training session was monitored by experienced PTs, ensuring that training intensities were in the prescribed range. In addition, the robust testing of Vo_{2peak} was a major strength.

Study limitations

The participants in this study were younger and had a higher Vo_{2peak} compared with other research conducted in the population with stroke.[26,27] The younger age might be explained by the fact that 2 of the 3 participating hospital units only treated patients 67 years or younger. The higher Vo_{2peak} can be explained by the rigorous test protocol and the respiratory exchange ratio values reported in our study, showing that true Vo_{2peak} levels were achieved. Another reason might be the fact that patients who are highly motivated to undertake physical activity and exercise are more likely to accept inclusion in a high-intensity training trial. However, compared with an age-matched healthy Norwegian population (50-59 years of age), who showed Vo_{2peak} levels of 3.61 ± 0.60 $L\cdot min^{-1}$ in men and 2.35 ± 0.38 $L\cdot min^{-1}$ in women, the participants in our study were deconditioned at baseline.[28]

Another limitation was that blood pressure and blood profiles were in the normal range at baseline, making it unlikely to achieve any differences between the groups regarding these outcomes. In future research, participants with normal or abnormal blood pressure and blood profile should be analyzed separately in subgroup analyses to study the potential effect of HIIT on these outcomes.

Furthermore, we did not collect information about the activity routines or follow-up services from health care personnel as part of standard care. It is also a limitation that some of the participants might have revealed their group assignment to the test personnel. However, to minimize this bias, the testing and training were performed at different locations, and participants in both groups were told not to reveal their group assignment to the test personnel. Finally, the post tests were performed within the first week after the last training session, which might have had an effect on the Vo_{2peak} tests in the intervention group. According to a study by Hatle et al[29] participants did not increase Vo_{2peak} when tested 4 days after the last training session compared with a 6% improvement when tested 12 days after the last session.

Conclusions

The present multicenter trial involving people with stroke did not confirm our hypothesis that an 8-week supervised treadmill HIIT program in addition to standard care was superior to standard care alone in improving Vo_{2peak} ($L\cdot min^{-1}$) 12 months after inclusion. Secondary results from the peak test showed a significant improvement from before to immediately after the intervention, which was maintained for 12 months for Vo_{2peak} ($mL\cdot kg^{-1}\cdot min^{-1}$). There was no difference between groups in blood pressure or blood profiles.

The training was well tolerated, with a high adherence to the intensity of training and no serious adverse events related to the test protocol or the intervention. To reduce the cardiovascular risk profile by increasing Vo_{2peak} and reducing modifiable risk factors, further studies are needed to determine if HIIT is superior to other exercise modalities and intensities in the population with stroke.

Suppliers

a. Polar A300; Polar Electro.
b. MetaMax II portable ergospirometry system; Cortex Biophysik.
c. Cardiopulmonary exercise treadmill test; Woodway.
d. Connex Pro BP 3400; Welch Allyn.
e. activPAL; PAL Technologies.
f. IBM SPSS Statistics version 25; IBM.

Keywords

Cerebrovascular disorders; Exercise; Rehabilitation; Stroke

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References

1. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:227-76.
2. Hankey GJ. Secondary stroke prevention. Lancet Neurol 2014;13:178-94.
3. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380:219-29.
4. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 2016;354:i3857.

5. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2532-53.
6. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. Cochrane Database Syst Rev 2016;3:CD003316.
7. Gjellesvik TI, Brurok B, Tjonna AE, Torhaug T, Askim T. Oxygen uptake during functional activities after stroke-reliability and validity of a portable ergospirometry system. PLoS One 2017;12:e0186894.
8. Keteyian SJ, Brawner CA, Savage PD, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 2008;156:292-300.
9. Nes BM, Vatten LJ, Nauman J, Janszky I, Wisloff U. A simple nonexercise model of cardiorespiratory fitness predicts long-term mortality. Med Sci Sports Exerc 2014;46:1159-65.
10. Crozier J, Roig M, Eng JJ, et al. High-intensity interval training after stroke: an opportunity to promote functional recovery, cardiovascular health, and neuroplasticity. Neurorehabil Neural Repair 2018;32:543-56.
11. Karlsen T, Aamot IL, Haykowsky M, Rognmo O. High intensity interval training for maximizing health outcomes. Prog Cardiovasc Dis 2017;60:67-77.
12. Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. European J Cardiovasc Prev Rehabil 2004;11:216-22.
13. Helgerud J, Høydal K, Wang E, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med sci sports exerc 2007;39:665-71.
14. Weston KS, Wisloff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. Br J Sports Med 2014;48:1227-34.
15. Gjellesvik TI, Brurok B, Hoff J, Torhaug T, Helgerud J. Effect of high aerobic intensity interval treadmill walking in people with chronic stroke: a pilot study with one year follow-up. Top Stroke Rehabil 2012;19:353-60.
16. Askim T, Dahl AE, Aamot IL, Hokstad A, Helbostad J, Indredavik B. High-intensity aerobic interval training for patients 3-9 months after stroke. A feasibility study. Physiother Res Int 2013;19:129-39.
17. Boyne P, Dunning K, Carl D, et al. High-intensity interval training and moderate-intensity continuous training in ambulatory chronic stroke: feasibility study. Phys Ther 2016;96:1533-44.
18. Vogler AJ, Rice AJ, Gore CJ. Validity and reliability of the Cortex MetaMax3B portable metabolic system. J Sports Sci 2010;28:733-42.
19. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128:873-934.
20. Staessen JA, Li Y, Hara A, Asayama K, Dolan E, O'Brien E. Blood pressure measurement anno 2016. Am J Hypertens 2017;30:453-63.
21. Taraldsen K, Askim T, Sletvold O, et al. Evaluation of a body-worn sensor system to measure physical activity in older people with impaired function. Phys Ther 2011;91:277-85.
22. Twisk J, Bosman L, Hoekstra J, Rijnhart J, Heymans M. Different ways to estimate treatment effects in randomised controlled trials. Contemp Clin Trials Commun 2018;10:80-5.
23. Ellingsen O, Halle M, Conraads V, et al. High-intensity interval training in patients with heart failure with reduced ejection fraction. Circulation 2017;135:839-49.
24. Moholdt TT, Amundsen BH, Rustad LA, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. Am Heart J 2009;158:1031-7.
25. Tjønna AE, Lee SJ, Rognmo Ø, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation 2008;118:346-54.
26. Globas C, Becker C, Cerny J, et al. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. Neurorehabil neural repair 2012;26:85-95.
27. Ivey FM, Stookey AD, Hafer-Macko CE, Ryan AS, Macko RF. Higher treadmill training intensity to address functional aerobic impairment after stroke. J Stroke Cerebrovasc Dis 2015;24:2539-46.
28. Loe H, Steinshamn S, Wisloff U. Cardio-respiratory reference data in 4631 healthy men and women 20-90 years: the HUNT 3 fitness study. PLoS One 2014;9:e113884.
29. Hatle H, Stobakk PK, Molmen HE, et al. Effect of 24 sessions of high-intensity aerobic interval training carried out at either high or moderate frequency, a randomized trial. PLoS One 2014;9:e88375.