Treadmill interval training after stroke

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 eight weeks of high-intensity interval training (HIIT) in addition to standard care would increase and maintain peak oxygen uptake ($\text{VO}_{2\text{peak}}$) 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 three Norwegian hospitals.

Participants: Participants, three months to five years after first-ever stroke, were randomly assigned to the intervention group ($n=36$) or the control group ($n=34$), 42% women, mean (SD) age was 57.6 (9.3) years and 26.4 (14.5) months post-stroke.

Intervention: The intervention was eight weeks, three times a week high-intensity interval treadmill training with work periods of 4x4 minutes at 85-95% of peak heart rate (HR_{peak}), interspersed with 3 minutes of active recovery at 50-70% of HR_{peak} . The control group received standard care according to national guidelines.

Outcomes: The primary outcome, analyzed by intention-to-treat, was $\text{VO}_{2\text{peak}}$ measured as liters per minute ($\text{L} \cdot \text{min}^{-1}$) 12 months after inclusion. Secondary outcome measures were blood pressure and blood profile.

Results: Mean (SD) baseline $\text{VO}_{2\text{peak}}$ was 2.63 (1.08) versus 2.87 (0.71) $\text{L} \cdot \text{min}^{-1}$, while at 12 months $\text{VO}_{2\text{peak}}$ was 2.70 (1.00) versus 2.67 (0.76) $\text{L} \cdot \text{min}^{-1}$, $p=0.068$, in the intervention and control groups, respectively. There was a significant and greater improvement in the intervention group compared to the control group at 12 months in three out of six secondary outcomes from the peak test, but no significant differences for the blood pressure or blood profile.

Conclusions: The HIIT intervention, which was well-tolerated in this sample of well-functioning stroke survivors, 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.

Keywords: stroke, cerebrovascular disease, rehabilitation, physical therapy, exercise, high-intensity training, long-term follow-up

List of selected abbreviations

BMI	Body mass index
CI	Confidence interval
HIIT	High-intensity interval training
HR	Heart rate
HR _{peak}	Peak heart rate
mRS	Modified Rankin Scale
SD	Standard deviation
VO ₂	Oxygen uptake
VO _{2peak}	Peak oxygen uptake

In the general population, substantial evidence from large epidemiological studies suggest that high levels of physical activity and exercise are beneficial for mitigating modifiable risk factors like 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, it has been shown that the majority of stroke survivors 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 stroke population.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 four 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 stroke population 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 eight-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 subacute and chronic stroke survivors. The secondary aim was to investigate the effects of HIIT on blood pressure and blood profiles. Our primary hypothesis was that an eight-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 three 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 to 22 participants were included at a time.

Inclusion criteria were first-ever stroke (ischemic or hemorrhagic) verified with CT/MR; willing and able to give informed consent, independent walking with or without an assistive device, minimum three months and maximum five 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 doctor and a score on the modified Rankin Scale (mRS) of 0-3. Exclusion criteria were instability of cardiac conditions (e.g., 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).

Intervention and control

Standard care

Participants assigned to the control group received standard care. The Norwegian guidelines recommend chronic stroke patients 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 high-intensity interval training. The training protocol was repeated three times per week for eight consecutive weeks, giving a total of 24 training sessions. Two participants trained at the same time on treadmills controlled by one 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 comprised 4-minute intervals (4x4) at 85-95% of HR_{peak} interspersed with 3 minutes of active breaks at 50-70% HR_{peak} . Total exercise time was 38 minutes. The exercise intensity was set based on the HR_{peak} from the VO_{2peak} test controlled with HR monitors (Polar A300, Polar Electro, Kempele, Finland). 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 out of the 24 training sessions as successfully adhering to the training protocol. If less than two high-intensity periods were completed, the training session was not considered to have been completed successfully.

After eight weeks of HIIT the participants were invited three 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 training at each hospital.

Outcomes

Participants were assessed at three time points: (1) at baseline, approximately one week before initiating the intervention, (2) at post-test, within one week after the eight-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 one week at each time point.

The primary outcome measure was $\text{VO}_{2\text{peak}}$ measured in liters per minute ($\text{L}\cdot\text{min}^{-1}$), assessed with a graded exercise treadmill test 12 month after inclusion. Secondary outcomes were $\text{VO}_{2\text{peak}}$ measured as milliliters per kilo ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), systolic and diastolic blood pressures measured on the non-affected arm at rest and blood profiles (i.e., lipid levels and insulin resistance) measured both at post-test and at 12 months. Heart rate (HR), lactate, minute ventilation (VE), respiratory exchange ratio (RER), Borg scale and carbon dioxide output (CO_2) 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 $\text{VO}_{2\text{peak}}$ measurements, the MetaMax II portable ergospirometry system (Cortex Biophysik, Leipzig, Germany) 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 $\text{VO}_{2\text{peak}}$, a cardiopulmonary exercise treadmill test (Woodway, Waukesha, WI, USA) with an individual ramp protocol was used. After a 10-15 min warm-up period, the speed was increased by $0.5\text{--}1.0\text{ kmh}^{-1}$ or the inclination by 1–2%, while the participant maintained a stable VO_2 for >30seconds. $\text{VO}_{2\text{peak}}$ was defined as the average of the three highest VO_2

measurements obtained during the incremental treadmill test. Reasons for terminating the test were subjective exhaustion or standard clinical criteria.¹⁹ HR_{peak} was the highest registered HR during the VO_{2peak} test.

Blood pressure was measured according to recommended procedures,²⁰ with an automated device (Connex Pro BP 3400, Welch Allyn, Skaneateles Falls, NY, USA), before the VO_{2peak}-test and after a five-minute seated rest period.²⁰ The mean of three consecutive measurements with an interval of one 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 (LDL), high-density lipoprotein (HDL), total cholesterol, triglycerides, glycosylated hemoglobin (HbA1c) 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 HR 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 (PAL Technologies, Glasgow, Scotland), attached to the participant's non-affected thigh for seven consecutive days immediately after baseline testing, post-test and follow-up. The activPAL has been validated in the stroke population.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 two previous pilot studies,^{15,16} we estimated a mean (SD) $\text{VO}_{2\text{peak}}$ to be 2.27 (0.45) $\text{L} \cdot \text{min}^{-1}$ at inclusion. As most intervention studies also report positive responses in the control group, we estimated a minimal improvement of 2% after the eight-week intervention period to 2.32 (0.44) $\text{L} \cdot \text{min}^{-1}$ and a 10% increase in $\text{VO}_{2\text{peak}}$ in the intervention group to 2.6 (0.55) $\text{L} \cdot \text{min}^{-1}$, 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 0.05. We expected a 10% drop-out 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 endpoints. As recommended by Twisk et al. (2018),²² we adjusted for baseline difference for the outcome of interest. We included indicator variables for the post-test 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. (2018).²²

Adherence to the intervention was estimated by calculating the mean (SD) percentage of HR during the final two 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 four consecutive 24-hour recordings from activPAL. The day of attachment of the activPAL was excluded from the analysis. IBM SPSS Statistics, version 25 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

We screened a total of 168 patients from the patient lists at the three 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 one discontinued due to a prescheduled surgery not related to the intervention protocol (Figure 1).

The mean (SD) 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 an mRS score ≤ 2 (Table 1).

For the primary outcome, the mean (SD) baseline $\text{VO}_{2\text{peak}}$ was 2.63 (1.08) versus 2.87 (0.71) $\text{L} \cdot \text{min}^{-1}$, while at follow-up $\text{VO}_{2\text{peak}}$ was 2.70 (1.03) versus 2.67 (0.76) $\text{L} \cdot \text{min}^{-1}$, $p=0.657$, in the intervention group and the control group, respectively (Table 2 and Figure 2).

Out of 792 planned training sessions, a total of 728 sessions were successfully completed (92%). Mean (SD) percentage of HR_{peak} ranged from 90.0 (4.6) to 93.8 (3.8) percent. Mean (SD) 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 group (Table 4).

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

Discussion

This is the first randomized controlled multicenter trial assessing the effect of HIIT on VO_{2peak} in a stroke population. The results showed that 24 sessions of treadmill HIIT for eight weeks was superior to standard care alone to achieve a higher VO_{2peak} ($L \cdot min^{-1}$) immediately after the intervention. However, the difference between the groups was not maintained at the 12-month follow-up.

As shown in Figure 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 4x4 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 HR_{peak} .¹¹ We ensured the intensity by having experienced PTs adjusting the treadmill speed and inclination to be within the prespecified HR intensity zone. This contrasts with previous research in the stroke population 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 to 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 passed away before the 12-month follow-up. Investigations from the medical doctor 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 stroke population.^{15,16}

A major strength of the present study was its being a high-quality multicenter trial with randomization of participants and blinded outcome assessment. The mixed-model statistical analyses have two advantages compared to 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 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. Thirdly, this method allows for adjustment of baseline values as recommended by Twisk et al. (2018).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 $\text{VO}_{2\text{peak}}$ was a major strength.

Study limitations

The participants in this study were younger and had a higher $\text{VO}_{2\text{peak}}$ compared to other research conducted in the stroke population.^{26,27} The younger age might be explained by the fact that two of the three participating hospital units only treated patients aged 67 years or younger. The higher $\text{VO}_{2\text{peak}}$ can be explained by the rigorous test protocol and the RER values reported in our study, showing that true $\text{VO}_{2\text{peak}}$ 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 to an age-matched healthy Norwegian population (50 to 59 years of age), who showed $\text{VO}_{2\text{peak}}$ levels of 3.61 (0.60) $\text{L}\cdot\text{min}^{-1}$ in men and 2.35 (0.38) $\text{L}\cdot\text{min}^{-1}$ 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 healthcare 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 impact on the VO_{2peak} -tests in the intervention group. According to a study by Hatle et al. (2014),²⁹ participants did not increase VO_{2peak} when tested four days after the last training session compared to 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 eight-week supervised treadmill HIIT training 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 with 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 stroke population.

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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**(1): 227-76.
2. Hankey GJ. Secondary stroke prevention. *Lancet Neurol* 2014; **13**(2): 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 (London, England)* 2012; **380**(9838): 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; a journal of cerebral circulation* 2014; **45**(8): 2532-53.
6. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. *The Cochrane database of systematic reviews* 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**(10): e0186894.
8. Keteyian SJ, Brawner CA, Savage PD, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *American heart journal* 2008; **156**(2): 292-300.
9. Nes BM, Vatten LJ, Nauman J, Janszky I, Wisloff U. A simple nonexercise model of cardiorespiratory fitness predicts long-term mortality. *Medicine and science in sports and exercise* 2014; **46**(6): 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. *Neurorehabilitation and neural repair* 2018; 1545968318766663.
11. Karlsen T, Aamot IL, Haykowsky M, Rognmo O. High Intensity Interval Training for Maximizing Health Outcomes. *Progress in cardiovascular diseases* 2017; **60**(1): 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 journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2004; **11**(3): 216-22.
13. Helgerud J, Høydal K, Wang E, et al. Aerobic high-intensity intervals improve VO₂max more than moderate training. *Medicine and science in sports and exercise* 2007; **39**(4): 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. *British journal of sports medicine* 2014; **48**(16): 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. *Topics in stroke rehabilitation* 2012; **19**(4): 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. *Physiotherapy research international : the journal for researchers and clinicians in physical therapy* 2013.
17. Boyne P, Dunning K, Carl D, et al. High-Intensity Interval Training and Moderate-Intensity Continuous Training in Ambulatory Chronic Stroke: Feasibility Study. *Physical therapy* 2016; **96**(10): 1533-44.
18. Vogler AJ, Rice AJ, Gore CJ. Validity and reliability of the Cortex MetaMax3B portable metabolic system. *Journal of sports sciences* 2010; **28**(7): 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**(8): 873-934.
20. Staessen JA, Li Y, Hara A, Asayama K, Dolan E, O'Brien E. Blood Pressure Measurement Anno 2016. *American journal of hypertension* 2017; **30**(5): 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. *Physical therapy* 2011; **91**(2): 277-85.
22. Twisk J, Bosman L, Hoekstra J, Rijnhart J, Heymans M. Different ways to estimate treatment effects in randomised controlled trials. *Contemporary clinical trials communications* 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**(9): 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. *American heart journal* 2009; **158**(6): 1031-7.
25. Tjønnå 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**(4): 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. *Neurorehabilitation and neural repair* 2012; **26**(1): 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. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2015.
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**(11): 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**(2): e88375.

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Table 1. Characteristics of participants at inclusion

	Intervention (n=36)	Control (n=34)
Age (years)		
mean (SD)	57.6 (9.2)	58.7 (9.2)
Range	41 to 71	34 to 72
Male, n (%)	21 (58.3)	20 (58.8)
Time since stroke, months (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)
Betablocker, 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)	174.2(10.4)	176.81 (7.9)
Weight (kg)	82.1 (15.6)	87.47 (18.6)

BMI (kg/m ²)	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)

SD, standard deviation; BMI, body mass index; mRS, modified Rankin Scale; m, meter; m/s, meter per second;

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 x
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>Estimate</i>	<i>95% CI</i>
Peak test								
VO₂								
(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 to 0.36
Follow-up	28	2.70	1.00	28	2.67	0.76	0.15	-0.01 to 0.32
VO₂								
(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
Follow-up	28	33.10	10.21	28	30.91	8.03	1.87	-3.65 to -0.66
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
Follow-up	28	163.04	18.17	28	163.29	15.23	-4.37	-9.40 to 0.66
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
Follow-up	28	89.40	26.95	28	91.04	28.39	-6.98	-13.06 to -0.91
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
Follow-up	28	9.75	3.25	26	8.87	3.18	1.07	-2.18 to 0.05
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
Follow-up	28	1.07	0.09	28	1.06	0.10	-0.03	-0.06 to 0.00
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
Follow-up	28	17.20	1.37	28	16.57	1.87	-0.61	-1.33 to 0.11
CO₂								
(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
Follow-up	28	2.90	1.07	28	2.78	0.95	-0.27	-0.04 to -0.05

**Blood
pressure**
Systolic
(mm/Hg)

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
Follow-up	28	135.90	14.39	27	136.11	17.06	2.32	-4.59 to 9.23

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Diastolic (mm/Hg)								
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
Follow-up	28	82.93	7.39	27	85.70	10.40	1.72	-2.99 to 6.42
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
Follow-up	22	14.34	1.09	25	14.54	1.41	-0.09	-0.32 to 0.50
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
Follow-up	23	4.24	1.00	26	4.65	0.90	0.03	-0.31 to 0.38
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
Follow-up	23	2.41	0.92	26	2.79	0.87	-0.04	-0.31 to 0.23
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
Follow-up	23	1.39	0.39	26	1.49	0.42	-0.12	-0.00 to 0.25
Triglycerids								
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
Follow-up	22	1.49	0.75	26	1.24	0.52	-0.41	-0.87 to 0.06
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
Follow-up	22	5.62	0.51	26	5.48	1.30	0.20	-0.49 to 0.09
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
Follow-up	22	958.36	453.18	25	873.30	455.85	78.96	-409.70 to 251.78

n, number of participants; SD, standard deviation; CI, Confidence Interval; VO₂, oxygen uptake; HR, heart rate; VE, minute ventilation; RER, respiratory exchange ratio; CO₂, carbon dioxide output; Hb, hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Notes:

The difference estimates are results from the baseline-adjusted linear mixed models (positive values favor intervention group).

Post = Post intervention assessment

Follow-up = 12 months follow-up assessment (12 months after randomization)

POST-PRINT

Table 3. Exercise intensity presented as percentage of peak heart rate during the last two 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 (3.7)	92.5 (2.8)	92.7 (4.5)
Borg's 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's 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's 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)

HR, heart rate; SD, standard deviation

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

Baseline	n	Intervention		n	Control		p-value
		Mean	SD		Mean	SD	
Time sitting/lying	32	18.94	1.06	29	19.09	1.50	0.64
Standing time	32	3.42	0.80	29	3.11	1.03	0.82
Stepping time	32	1.64	0.60	29	1.80	0.67	0.33
Step count	32	7321.6	3517.1	29	8481.4	3445.1	0.20
Transitions	32	54.84	19.92	29	54.25	15.53	0.90
Post-test							
Time sitting/lying	31	18.89	1.58	27	18.66	1.86	0.61
Standing time	31	3.55	1.08	27	3.48	1.35	0.82
Stepping time	31	1.55	0.69	27	1.86	0.71	0.10
Step count	31	6903.5	3311.6	27	8621.0	3672.7	0.07
Transitions	31	52.10	15.54	27	54.01	16.24	0.65
Follow-up							
Time sitting/lying	27	18.48	1.94	28	19.20	1.65	0.14
Standing time	27	3.89	1.38	28	3.01	1.10	0.01
Stepping time	27	1.63	0.77	28	1.79	0.71	0.42
Step count	27	6835.7	3774.7	28	8334.7	3817.3	0.15
Transitions	27	47.58	12.66	28	50.63	15.01	0.42

n; number of participants, SD; standard deviation

Figure Legends

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

Figure 2. Mean $\dot{V}O_{\text{peak}}$ in $\text{L}\cdot\text{min}^{-1}$ at baseline, post-test and follow-up. Error bars represent SD.

POST-PRINT