Journal Pre-proof

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PII: S0003-9993(20)30528-1

DOI: https://doi.org/10.1016/j.apmr.2020.07.012

Reference: YAPMR 57934

To appear in: *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION*

Received Date: 14 February 2020

Revised Date: 6 July 2020

Accepted Date: 15 July 2020

Please cite this article as: József T, Nagy F, Csutorás B, Prontvai N, Nagy Z, Török K, Blényesi E, Vajda Z, Farkas D, Tóth BE, Repa I, Moizs M, Sipos D, Kedves A, Kovács Á, Hortobágyi T, High frequency and intensity rehabilitation in 641 sub-acute ischemic stroke patients, *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION* (2020), doi: https://doi.org/10.1016/j.apmr.2020.07.012.

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Running Head: Reducing mobility-limitations in stroke

Ethics Committee approved the study protocol that was registered (NCT03736200)

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Abstract

Objective: To determine the effects of Exergaming on quality of life (QoL), motor, and clinical symptoms in sub-acute stroke patients.

Design: A pseudo randomized clinical trial, using a before-after test design.

Settings: University hospital setting.

Participants: Of 3,857 sub-acute, ischemic stroke outpatients, 680 were randomized and 641 completed the study.

Interventions: We determined the effects of 5x/week twice (EX2, 50 sessions, n=286) and once daily (EX1, 25 sessions, n=272) Exergaming and low-intensity standard care (CON, 25 sessions, n=83) on clinical, mobility, blood pressure (BP), and QoL outcomes.

Main Outcome Measures: The primary outcome: Modified Rankin Scale (mRS). Secondary outcomes: Activities of daily living (ADL), five aspects of health-related QoL(EQ-5D), Beck Depression Inventory (BDI), six-minute walk test (6MWT), Berg Balance Scale (BBS) and static balance (center of pressure, COP).

Results: During exercise, peak heart rate was 134, 134, and 126 $b \cdot min^{-1}$ in EX2, EX1, and CON. mRS improved similarly in EX2 (-1.8, effect size, d=-4.0) and EX1 (-1.4, d=-2.6) but more than in CON (-0.7, d=-0.6). QoL, Barthel index, Berg balance scale, six-minute walk test, and standing posturography improved in a pattern of EX2>EX1=CON. Systolic and diastolic rBP decreased more in EX2 and EX1 than CON. The intervention effects did no differ between males (n=349) and females (n=292).

Conclusion: Twice daily compared with once daily high-intensity Exergaming or once-daily lower intensity standard care produced superior effects on clinical and motor symptoms, BP, and QoL in male and female sub-acute ischemic stroke participants.

Key words: Virtual reality; Exercise; Quality of life; Activities of daily living; Gender

Abbreviations

ADL, activities of daily living

ANOVA, analysis of variance

BBS, Berg balance scale

BI, Barthel index

BDI, Beck depression inventory

BMI, body mass index

BP, blood pressure

CON, control group, receiving one standard physical therapy session daily, 5 days per week for 5 weeks (25 sessions)

COP, centre of pressure

DBP, diastolic blood pressure

EEG, electroencephalography

EQ5-VAS, 100 mm visual analogue measure of health-related quality of life

EQ-5D, EuroQol questionnaire, measuring health-related quality of life

EX2, Two Exergaming sessions daily, 5 days per week for 4 weeks (40 sessions)

EX1, One Exergaming session daily, 5 days per week for 4 weeks (20 sessions)

F, female gender

HR, heart rate

M, male gender

MMSE, mini mental state examination

mRS, modified Rankin Scale

MS, multiple sclerosis

NEO, COP path while standing in a narrow stance with eyes open

NEC, COP path while standing in a narrow stance with eyes closed

PD, Parkinson’s disease

PwS, People with Stroke

$p\eta^2$, partial eta squared

rBP, resting blood pressure

rDBP, resting diastolic blood pressure

rHR, resting heart rate

RPE, rate of perceived exertion

rSBP, resting systolic blood pressure

6MWT, six minute walk test

SBP, systolic blood pressure

SD, standard deviation

SPSS, Statistical Package for the Social Sciences

WEO, COP path while standing in a wide stance with eyes open

WEC, COP path while standing in a wide stance with eyes closed

While stroke incidence and mortality in Western European countries have been declining, in Central-Eastern Europe these rates are still increasing (1). In 2009, the incidence of stroke was 43.3/10,000 people in Hungary, twice the rate in Italy and Finland. The high incidence produces 10% of all deaths and high disability-adjusted life-years (DALY) scores (2). Even though policy-makers recognize the importance of prevention in developing countries, most of these efforts are ineffective, leaving people with stroke (PwS) with the next best option: reducing symptoms and risks for recurrent strokes.

Recommendations for sub-acute stroke participants' exercise rehabilitation advise therapists toward moderate intensity exercise (3,4). Recent trends, however, emphasize exercise intensity in the rehabilitation of a number of patient groups, including Parkinson's disease (PD) (5,6), multiple sclerosis (7), spinal cord injury (8), and stroke (9,10) and also after ischemic heart attacks (11). Heart rates (HR) above 60% of age-predicted maximum and rates of perceived exertion (RPE) over 15/20 denote high exercise intensity. Another marker of high exercise intensity is frequency, i.e., consecutive daily sessions or even multiple sessions within a day (12). This latter paradigm has not been systematically tested in the rehabilitation of PwS. There is also considerable debate whether exercise specific or not specific to mobility impairments should be used in sub-acute stroke participants' rehabilitation and to what extent technology should be incorporated (3,13-17). Indeed, implicitly learning and re-learning stepping and balance sequences in a technology-aided gaming environment seems to accelerate neurological patients' exercise-based rehabilitation (17-20) with the effects lasting for months in PD (21).

Sex differences in the responsiveness to exercise rehabilitation in sub-acute stroke participants are an understudied area due to small sample sizes and differences in hormonal profiles, age, and mortality between male and female PwS (22,23). The effectiveness of physical exercise in reducing risks for first and recurring strokes is higher in males than females and the responsiveness to exercise for improving clinical functions after a stroke tends to be higher for males than females (24,25).

The purpose of the present pseudo randomized clinical trial was to determine and compare the effects of an unusually high intensity and frequency Exergaming mobility rehabilitation program on sub-acute stroke participants' clinical symptoms, BP, mobility, and quality of life. Intensity was set by HR and RPE and also by within-day session frequency. One group attended the program twice daily for a total of 50 high-intensity Exergaming sessions. A second group attended one high-intensity Exergaming session per day for a total of 25 visits. A third group received low-intensity standard care in 25 sessions. We hypothesized that all programs would be effective but based on favorable experience with other patient groups in terms of responsiveness and adherence (5,13,14,21,26-28), we expected a hierarchical response pattern according to exercise intensity and frequency.

METHODS

Design and participants

This is an assessor-blinded, pre-post, pseudo randomized clinical trial. Using a consecutive selection from the hospital's medical records, a neurologist identified and examined participants for admission to the study conducted during the period from September 2014 to September 2018.

Patients admitted to the emergency department with a suspected stroke underwent a neurological exam, which included the National Institutes of Health Stroke Scale. This examination helped to determine, among others, the level of impairment in mobility and sensory function (range: 6-21, median: 16).

All participants were outpatients. Inclusion criteria: First-ever ischemic stroke diagnosed by a neurologist based on CT or MRI scans; time after stroke 2 to 4 weeks; mobility and postural limitation determined by neurological exam, and a modified Rankin Scale (mRS) score ≥ 2. Exclusion criteria: A history of multiple strokes; systolic resting blood pressure (BP) <120 or >160 mm·Hg; orthostatic hypotension; carotid artery stenosis; severe heart disease; hemophilia; traumatic brain injury; seizure disorder; uncontrolled diabetes**;** abnormal EEG; Mini Mental State Examination (MMSE) score <22; an abnormal blood panel; use of sedatives; irregular medication schedule; serious aphasia (Western Aphasia Battery, ≤25); serious visual or hearing impairments; serious sensory dysfunction; serious orthopaedic problems; neurological conditions affecting motor function (PD, multiple sclerosis [MS], multiple system atrophy, Guillain–Barré syndrome); alcoholism; recreational drug use; smoking after stroke diagnosis; inability to walk a minimum of 100 m with or without a walking aid in six minutes; Berg Balance Scale (BBS) score ≤32; Barthel Index (BI) score ≤70; inability to understand verbal instructions or prompts from a TV screen or current participation in a self-directed or formal group exercise program other than standard physical therapy.

Fig. 1 shows the flow of participants. Those who did not consent to be randomly assigned to Exergaming, were assigned to the control group (CON). These individuals were motivated for and interested in receiving rehabilitation but were unwilling to be randomized. The remaining participants were randomized to one session per day (EX1) or two sessions per day (EX2) high-intensity Exergaming. A physical therapist not involved in the trial performed the concealed randomization by drawing a colored ribbon from a covered box and attached one ribbon to each patient folder. Before the start of the study, all participants were enrolled in standard physical therapy provided by government insurance. EX1 and EX2 stopped this care and CON continued to receive this care. Participants gave written informed consent and the Institutional Research Ethics Committee approved the study protocol that was registered (NCT03736200).

<u>Outcomes</u>

Primary and secondary outcomes were measured before and after the interventions by the same certified physical therapists who were blinded to intervention allocation and were trained by the primary investigator. The testing order was standardized among participants and testing sessions. Pretests and posttests were performed within 1 week of the intervention. Patients were instructed not to drink caffeinated drinks 2h before measurements or exercise. The primary outcome was mRS, which measures independence in activities of daily living (ADLs) and discriminates among less severe levels of disability. mRS is a reliable and valid measure and is sensitive to change over time. A change of one unit in mRS is considered clinically meaningful (29-31).

Secondary outcomes addressed life domains. These tests are reliable, valid, and are sensitive to change over time in PwS. BI measures ADL performance. EQ-5D measures five aspects of health-related QoL. The Beck Depression Inventory (BDI) measures depression. BBS measures fall risk. The six-minute walk test (6MWT) measures fitness and walking capacity. Therapists equipped with a stopwatch, administered this test in a 50-m-long hallway that had wide tape marks on the floor every 10 m and short, thin tape marks every 2 m, within which the distance walked was measured by a measuring tape to the nearest cm as patients stopped at 6 min. Patients were not verbally encouraged during the test because in our experience some patients responded negatively to the stress associated with the performance demand by freezing and becoming confused. Instructions were: ‘Walk as far as you safely can for 6 min. Stop only when instructed at 6 min.’ There were no falls or medical emergencies during this test. Static balance was measured by the center of pressure (COP) path in standing on a force platform in the following order and conditions: 1) wide stance eyes open, 2) wide stance eyes closed, 3) narrow stance eyes open, and 4) narrow stance eyes closed for 20s, one trial each (Posture Evaluation Platform, MED-EVAL Ltd., Budapest, Hungary). Resting HR (rHR, Polar model RS800CX HR watch; Polar Electro Co. Ltd., Kempele, Finland) and resting BP (Omron M7 Intelli IT, OMRON Healthcare UK Ltd., Milton Keynes, UK) were measured in sitting 10 minutes before and after each session and peak HR was measured during each exercise session. In Visit 1 participants became familiar with Exergaming by watching and performing modules and completed questionnaires. Visit 2 included the measurements of body height and mass, COP, and 6MWT.

<u>Interventions</u>

EX2 exercised twice daily at 8.00-9.00h and 14.00-15.00h. The 1-h-long sessions comprised 5 minutes of warm-up, 25 minutes of Exergaming, 25 minutes of agility training, and 5 minutes of cool-down. The intervention consisted of 5 consecutive sessions per week for 5 consecutive weeks, i.e., 50 sessions for EX2 and 25 sessions for EX1 in the hospital’s outpatient physical therapy gym. In EX2 and EX1 exercise intensity was set in each session to a rate of perceived exertion (RPE) of 14-16/20. RPE was also recorded in CON. EX1 and EX2 performed the same program except that EX2 performed it twice per day.

Two physical therapists, who did not perform the assessments, delivered the interventions for groups of 6–8 participants who exercised barefoot on soft gym mats. Warm-up included spinal mobilization, stabilizing exercises, and stepping patterns, and gait variations. Exergaming used three modules of the Xbox 360 core system. Reflex Ridge prompts users to reflexively respond to visual stimuli. Space Pop prompts performers to reach targets with the extremities and the entire body to improve spatial orientation. Just Dance prompts users to generate and combine movement sequences, illustrated previously by video clips (5). The agility component included the manipulation and transport of hand-held sensory tools, weighted bars, fitness balls, and Pilates equipment. These routines require attention, executive function, and high speed of cognitive processing of oncoming visual and auditory cues, affording a high cognitive load. The program also provides a strong neuromuscular stimulus due to ever-changing sensory environment (soft/hard surfaces, weighted/unweighted implements, slow/fast movement execution, reactive/self-initiated responses to cues). Cool-down included walking and breathing exercises. CON received government-prescribed standard care, which includes daily 30 minutes of group exercises in sitting and 30 minutes of individual physical therapy using walking and balance exercises at local clinics. Exercises in sitting target upper extremity and trunk muscle strength by lifting, lowering, and rotating medicine balls and end-weighted sticks. Exercise in standing targeted lower extremity function, including stepping variations (forward, backward, diagonally while standing on one leg), weight shifting, coordinative movements with arms while walking with and without various sensory implements, squatting movements with arm support on chairback to strengthen the lower extremity extensor mechanism. After the exercise sessions, every participant in each group received 20 minutes of medical massage of the lower extremities. We asked participants to record their symptoms in a log that was checked by therapists daily and not to change their diet, medication, or physical activity habits for the duration of this study.

<u>Statistical analyses</u>

Data are expressed as mean ±SD. Variables were checked for normal distribution with the Shapiro–Wilk test. We compared EX2, EX1, and CON at baseline using a one-way parametric or a Kruskal-Wallis ANOVA. We interpreted Group (EX2, EX1, CON) by Sex (males, females) interactions on the post minus pre absolute change scores as a Group by Sex by Time interaction. We used Tukey's post-hoc contrast to identify the means that were different at $p<0.05$. The effect sizes for Group, Sex, and Group by Sex effects were characterized by partial eta squared ($p\eta^2$). We used Cohen's within group effect size, d (small: 0.20; moderate: 0.50; large: 0.80), to determine the size of the effects over time. The Holm method was used to correct for family-wise error.

RESULTS

<u>Participant characteristics</u>

Table 1 shows the frequency, medical, and co-morbidity data for the 349 male and 292 female (n=641) PwS enrolled in the study 2.9 (±0.75) weeks after an ischemic stroke. In both sexes, ~50% or 326 strokes occurred in the left hemisphere, followed by a stroke in the cerebellum, brainstem, or the right hemisphere. No participant had more than two of the 23 most common co-morbidities of which of hypertension (27%), ischemic heart disease (19%), and atherosclerosis

(10%) occurred at the highest rates. 54% of males and females smoked and ~32% of participants consumed 1-3 drinks per day. 93% of participants took medications. A similar proportion of participants in each group took antihypertensive drugs, including thiazide diuretics (38-45%), calcium channel blockers (15-20%), angiotensin-converting enzyme inhibitors (10-15%), angiotensin receptor blockers (10-15%), or received polytherapy by taking three or more drug classes (18-22%). The type and frequency of other drugs participants took were not available.

<u>Intervention effects</u>

Groups and sexes were similar at baseline (Table 2). The 1.8 points (±0.81; d=4.0) and 1.4 points (±0.95; d=2.6) improvements in mRS in EX2 and EX1, respectively, did not differ but exceeded the -0.7 points (±0.73; d=0.6) change in CON (Group main effect: $p<0.001$, Table 3, Fig. 2). Except for body weight, sex did not affect the intervention-induced changes. Males lost more weight (-6.0% ±8.69, d=-1.1) than females (1.3% ±9.94, d=0.20) but males vs. females lost more weight in EX1 (males: -6.5% ±8.54 vs. females: 2.1% ±9.92) and CON (males: -5.9% ±10.53 vs. females: 11.5% ±14.94) compared with EX2 (males vs. females: n.s.). Improvements in BI differed ($p<0.001$) among groups (EX2: d=5.6, EX1: d=2.9, CON: d=1.2). EQ5-VAS (but not EQ5-Sum) improved in EX2 (d=1.6) more ($p<0.05$) than in EX1 (d=0.8) or CON (d=0.7). Improvements in BBS differed ($p<0.001$) among groups (EX2: d=2.2, EX1: d=1.4, CON: d=1.2). Improvements in 6MWT differed ($p<0.001$) among groups (EX2: d=2.9, EX1: d=2.7, CON: d=1.6). The COP path revealed a uniform Group main effect in WEO, WEC, NEO, and NEC (all $p\leq0.018$): in these four measures combined EX2 shortened COP path (d range: -1.2 to -2.4) more than EX1 and CON. No changes occurred in MMSE, DBI, and EQ5-SUM.

Intervention effects on HR, BP, and RPE

Sex did not affect any of the changes. The results below are presented for data pooled across 25 days. rHR increased ($p<0.001$, $p\eta^2=0.11$) in each group (d=1.2 to 2.2) but more in EX2 and EX1 vs. CON (Table 4). rSBP decreased (d=0.8 to 2.4) in all groups ($p=0.001$, $p\eta^2=0.41$) but more in EX2 and EX1 than CON. In EX2, from before Session 1 to after Session 2, the total reduction in rSBP was 4.2 mm·Hg (p=0.001, d=2.6) or 3.2% (±4.08). rDBP decreased (d=1.3 to 3.7) in all three groups ($p=0.001$, $p\eta^2=0.63$) but more in EX2 and EX1 than CON. In EX2, from before Session 1 to after Session 2, the total reduction in rDBP was 5.8 mm·Hg (p=0.001, d=3.2) or 5.8% (±6.08). Peak HR during exercise was lower ($p=0.001$; $p\eta^2=0.48$) in CON than EX2 and EX1. RPE during exercise was lower ($p=0.001$; $p\eta^2=0.96$) in CON than EX2 and EX1. Peak HR and RPE did not differ between EX2 and EX1.

DISCUSSION

We compared the effects of high intensity and frequency agility Exergaming and lower intensity standard care programs on clinical symptoms, mobility, BP, and QoL in PwS. Due to an ischemic stroke ~3 weeks earlier, PwS (n=641) had explicit walking limitations but completed all sessions without adverse events. The preponderance of evidence supported the hypothesis: Twice daily compared with once daily high-intensity Exergaming or once-daily lower intensity standard care produced superior effects on clinical and motor symptoms, BP, and QoL in male and female sub-acute ischemic stroke participants (Figs. 2, Tables 3,4, Supplemental Digital Content S1).

Primary outcome

We included sub-acute (2 to 4 weeks after stroke) instead of chronic PwS who have greater potential for responsiveness to exercise therapy. The 3.4 mRS and 56.1 BI score at baseline indicated that participants had moderately severe ADL-specific disability (Table 1). However, walking disability was severe because the ~182m (n=641) distance over 6 minutes is the shortest among age- and sex-similar PD (232m) and MS patients (240m), older adults with mobility disability (334m), and healthy older adults (529m) (13,14,26). Despite sub-acute status, severity of disability, and moderate hypertension (Table 2), intensive and frequent exercise proved to be an effective therapy option for these subacute PwS (32).

Improvements of 1.8 (EX2) and 1.4 (EX1, Table 3) in mRS, the primary outcome, exceeded the clinically meaningful change of one unit irrespective of sex (29-31). Against expectations these changes in mRS were the only improvements that did not differ between the twice vs. once-daily interventions. Perhaps the sensitivity of mRS has a ceiling at once-weekly training or a total of 25 sessions (29-31). Only a handful of studies have examined the effects of high intensity exercise on mRS in sub-acute PwS but the gains we observed were much greater. For example, Exergaming plus standard therapy (n=100) compared with standard therapy (n=100) for seven consecutive days for 1h/day improved mRS by 0.58 vs. 0.23, respectively in sub-acute PwS who suffered a stroke 7 days earlier (33). Likewise, high intensity physical exercise 48h after a stroke (n=86) improved mRS at 3 months follow-up more than standard (n=80) or very early mobilization 24h after a stroke (n=82) (34). The data suggest that high intensity exercise therapy especially with an Exergaming element is effective for improving ADL independence in sub-acute PwS but such improvements can be especially sizeable if therapy is administered twice daily (Table 3). The intervention effects in the present study could be also greater than in previous studies because in those the time after post-stroke was 1-7 days, whereas we started the intervention 3 weeks post-stroke on average. We found no evidence for the responsiveness to exercise in terms of rMS being higher in males than females (24,25).

Secondary outcomes

Secondary outcomes addressed life domains, which all improved by a clinically meaningful margin in the expected hierarchical response pattern according to exercise intensity and frequency (Fig. 2, Table 3). BI measures the perceived ability to perform ADLs, which improved by 8-9 points, strongly favouring exercise intensity and frequency vs. standard care. The improvements in 6MWT were particularly impressive because PwS in EX2 walked ~125m longer distance than at baseline. This gain was nearly twice ~~of~~ the gain in the lower frequency (EX1) and intensity (CON) groups (Table 3). These changes are substantially greater than the highest change of 37m reported in a meta-analytic review of four studies also using high-intensity but not twice-daily training (32). The improvements in BI, BBS, 6MWT, and standing balance were paralleled by changes in EQ5-VAS, implying that participants perceived an increase in their QoL due to being more effective in executing ADLs, lower likelihood of a fall, greater walking ability and fitness, and higher standing stability. The changes contrast with a lack of reductions in depression, which might have been too low at baseline to reflect improvements from exercise.

Participants had Stage 1 hypertension (130/89mm·Hg) with a somewhat elevated rHR (86 $b\cdot min^{-1}$, Table 2). As expected, rHR was about 10 $b\cdot min^{-1}$ elevated 10min after exercise but SBP and especially DBP decreased 10min after exercise. More importantly, rBP chronically decreased by up to ~4 to 6 mm·Hg in EX2. The acute reductions in rBP are related to the postexercise hypotension, which can last up to 24h after an exercise bout in PwS (35). Because SBP at the start of the 25th session was ~5 mm·Hg lower than at the start of the EX2 program (131mm·Hg, Supplemental Digital Content S1), the exercise program afforded an anti-hypertension benefit, which is most likely due to a reduction in peripheral resistance (35). Such reductions in rBP pressure are known to reduce risks for a recurrent ischemic event. Our data are in clear support of recent recommendations for prescribing vigorous-intensity exercise for hypertensive adults (35).

<u>Exercise intensity</u>

A novel element of the present study was the use of twice-daily exercise sessions. Our rationale was that most PwS in the early, sub-acute phase of recovery respond~~s~~ well to exercise stimuli. The ensuing adaptations induce brain plasticity in a dose-dependent manner that last beyond the immediate training period and underlie motor recovery (36). The unusual twice-daily paradigm does indeed go against recent recommendations. For example, a meta-regression of exercise frequency revealed that high frequency was actually associated with a reduced effect on a number of outcomes in PwS (37). The conceptual basis for using low vs. high exercise frequency for sub-acute PwS's mobility treatment is that patients need to rest for neuroplasticity to emerge, allowing them to learn new and re-learn impaired movements (37). However, we did not observe any signs that the high exercise frequency and intensity (Table 4) would have interfered with clinical or motor adaptations. Just the opposite: in 5 of 6 outcomes EX2 improved the most compared with EX1 and CON. In addition, neurological patients are physically so deconditioned that PwS adapt rapidly to the high-intensity stimulus, which in fact facilitates motor learning even if the conditioning stimulus is not specific to a given motor deficit (3,13-17). This could be the reason for uniform increases across the outcomes (Table 3). However, we point out that there is also evidence in support of low intensity exercise being effective to improve gait and balance in PwS, increasing participants' treatment options (38).

Limitations

While stroke prevalence is highest among older females who are underrepresented in exercise trials, we also were unable to include such PwS. A lack of difference between groups in the outcomes at baseline dampens the severity of the limitation that the study was a pseudo and not a fully randomized trial, which could bias the results for CON. We did not control physical activity and diet. Indeed, males were 7 kg heavier than females at baseline (Table 1). While males lost ~5 kg, females were weight-stable or gained weight up to ~7kg (Table 3), implying an interaction between diet or physical activity or both and sex. PwS often present with fatigue but we did not measure it (3). While the 95% adherence and 5% dropout make high exercise intensity feasible, therapists delivered exercise sessions in a hospital facility. Many PwS have no access to such facilities, a setting that counters trends to reduce care costs by having PwS exercise at home. However, the efficacy of high intensity rehabilitation of sub-acute PwS at home is uncertain (10). Assessors were blinded to participants' group assignment but we did not assess if the blinding was maintained and assessments remained unbiased. It is unclear if the current paradigm is feasible in a home setting using remote monitoring and off-the-shelf technology. Without neural, biomechanical or behavioral markers, we were unable to determine the mechanisms of improvements in clinical and motor symptoms.

Conclusions

Twice-daily compared with once-daily high-intensity Exergaming or once-daily lower intensity standard care produced superior effects on clinical and motor symptoms, BP, and QoL in male and female sub-acute stroke participants.

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Figure 1. Flow of participants.

Figure 2. Improvements in primary (mRS, modified Rankin Score, shaded gray) and secondary outcomes after twice-daily Exergaming (50 sessions, EX2), once-daily Exergaming (25 sessions, EX1), and once-daily standard care physical therapy (25 sessions, CON) on 5 consecutive days for 5 consecutive weeks. (BI, Barthel Index; EQ5-VAS, health-related quality of life visual analogue scale; BBS, Berg Balance Scale; 6MWT, six-minute walk test; COP, center of pressure path). In each outcome the changes in the three groups were significantly different from one another ($p<0.05$).

Supplemental Digital Content S1. Resting systolic blood pressure before (filled symbols) and after (open symbols) Sessions 1 (A) and 2 (B) and resting diastolic blood pressure before and after Sessions 1 (C) and 2 (D) in the twice daily Exergaming (EX2) group (n = 283)

- Participants ~3 weeks after an ischemic stroke were able to exercise at a high intensity twice a day for 25 consecutive days without adverse events

- Clinical symptoms, blood pressure, motor function, and quality of life improved most after high intensity twice-daily vs. high intensity once-daily virtual reality training or low intensity standard care

- Exercise prescription of acute ischemic stroke patients could include high intensity and high frequency exercise aided by technology

- Future studies will examine how the feasibility of such rehabilitation programs in a home environment supported by remote monitoring

Table 2. Group and sex comparisons at baseline.

		EX2		EX1		CON		All	
Variable	Sex	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Age, y	M	67.5	5.44	65.6	6.10	65.2	6.10	66.4	5.89
	F	67.7	5.56	66.2	6.10	64.7	5.49	66.7	5.86
	Both	67.6a	5.49	65.9	6.10	64.9	5.80	66.5	5.87
Height, cm	M	177.3	5.26	178.1	4.48	177.9	4.23	177.7	4.81
	F	169.2	4.10	170.0	4.00	169.8	2.96	169.6b	3.94
	Both	173.6	6.25	174.4	5.87	174.3	5.50	174.0	6.00
Mass, kg	M	76.6	8.17	77.3	7.56	77.3	8.41	77.0	7.93
	F	72.0	6.93	70.4	7.88	64.0	6.68	70.3	7.72
	Both	74.5	7.95	74.2	8.41	71.4	10.15	74.0	8.50
BMI, $kg \cdot m^{-2}$	M	24.4	2.76	24.4	2.30	24.4	2.41	24.4	2.52
	F	25.2	2.78	24.4	2.88	22.2	2.38	24.5	2.93
	Both	24.8	2.79	24.4	2.57	23.4	2.63	24.4	2.71
MMSE	M	27.2	1.31	26.9	1.45	27.0	1.33	27.0	1.37
	F	26.9	1.53	27.1	1.49	27.1	1.34	27.0	1.49
	Both	27.1	1.41	27.0	1.47	27.0	1.33	27.0	1.43
HR, $b \cdot min^{-1}$	M	89.8	9.86	83.2	5.88	83.6	5.26	86.2	8.46
	F	87.5	8.88	83.6	6.07	83.6	5.07	85.4	7.60
	Both	88.7	9.47	83.4	5.96	83.6	5.15	85.8	8.08
SBP, mm·Hg	M	131.6	8.86	129.5	8.47	134.1	8.81	131.0	8.80
	F	130.5	9.57	127.8	6.32	131.6	8.97	129.5	8.37

	Both	131.1	9.19	128.7	7.61	133.0	8.91	130.3	8.64
DBP, mm·Hg	M	87.5	6.84	88.4	7.70	90.5	7.40	88.3	7.33
	F	89.5	7.95	89.0	8.36	94.6	6.08	90.0	8.09
	Both	88.4	7.43	88.7	8.00	92.3	7.10	89.0	7.73
BI	M	56.1	8.01	55.6	8.67	58.3	6.52	56.2	8.14
	F	56.4	8.11	55.0	8.87	57.3	8.05	55.9	8.44
	Both	56.2	8.04	55.4	8.75	57.8	7.21	56.1	8.28
BDI	M	12.2	3.03	12.4	2.80	12.0	3.06	12.2	2.93
	F	12.9	2.93	12.6	2.82	12.7	2.60	12.7	2.84
	Both	12.5	3.00	12.5	2.81	12.3	2.87	12.5	2.90
EQ5-VAS, mm	M	63.6	9.42	65.0	9.51	60.8	9.47	63.8	9.53
	F	63.6	9.43	64.1	9.64	66.0	6.11	64.1	9.17
	Both	63.6	9.41	64.6	9.56	63.1	8.50	63.9	9.37
EQ5-Sum	M	13.1	1.75	13.6	1.69	13.7	1.65	13.4	1.73
	F	13.7	1.65	13.6	1.61	14.0	1.68	13.7	1.64
	Both	13.4	1.74	13.6	1.65	13.8	1.66	13.5	1.70
BBS	M	22.1	4.40	23.2	4.51	22.3	4.68	22.6	4.50
	F	22.2	4.60	22.8	4.91	21.8	4.11	22.4	4.68
	Both	22.2	4.49	23.0	4.69	22.1	4.42	22.5	4.58
6MWT, m	M	179.9	48.50	183.1	48.05	171.2	55.37	180.1	49.26
	F	188.5	43.91	181.2	45.41	185.1	43.60	185.0	44.49
	Both	183.9	46.56	182.2	46.80	177.4	50.65	182.3	47.17
COP path, cm									

WEO	M	8.8	5.95	7.5	4.68	7.8	3.88	8.1	5.22
	F	5.8	3.34	7.9	4.93	7.7	4.31	6.9	4.31
	Both	7.4	5.14	7.7	4.79	7.8	4.05	7.6	4.86
WEC	M	10.4	5.25	8.0	4.19	9.5	6.03	9.2	5.06
	F	6.4	4.14	8.6	4.46	7.9	5.93	7.5	4.64
	Both	8.5	5.16	8.3	4.31	8.8	6.00	8.5	4.94
NEO	M	9.2	5.81	8.4	5.37	8.4	4.72	8.7	5.49
	F	8.3	5.40	8.7	4.51	9.7	6.44	8.6	5.20
	Both	8.8	5.64	8.5	4.99	9.0	5.56	8.7	5.36
NEC	M	11.0	6.01	9.6	5.36	10.2	6.29	10.3	5.80
	F	10.0	6.15	10.6	5.99	10.0	4.26	10.3	5.86
	Both	10.6	6.08	10.1	5.66	10.1	5.45	10.3	5.82

EX2, Two Exergaming sessions daily, 5 days per week for 5 weeks (50 sessions)

EX1, One Exergaming session daily, 5 days per week for 5 weeks (25 sessions)

CON, One standard physical therapy session daily, 5 days per week for 5 weeks (25 sessions)

M, Males

F, Females

a, EX2 different from EX1 and CON

b, Males different from females

BMI, body mass index

MMSE, Mini-Mental State Examination (range: 0 to 30, higher is better)

BI, Barthel Index (0 to 100, 0-20: total dependency, 21-60: severe dependency: 61-90: moderate dependency, 91-99: slight dependency

BDI, Beck depression inventory (0-63, 0-7: normal; 8-12: mild depression; 13-17: moderate depression; >18: severe depression.

EQ5-VAS, 100 mm visual analogue measure of health-related quality of life (higher score, a better perceived quality of life)

EQ5-Sum, sum of the EuroQol questionnaire mobility, self-care, usual activities, pain/discomfort, and anxiety/depression sub-scales, each scored 1-5 (worst-best), with 5 being the best and 25 the worst score

BBS, Berg Balance Scale (0 to 20: high fall risk; 21-40: medium fall risk; 41–56 (maximal score) = low fall risk

6MWT, six-minute walk test

COP, centre of pressure, lower values denote less sway in cm

WEO, COP path while standing in a wide stance with eyes open

WEC, COP path while standing in a wide stance with eyes closed

NEO, COP path while standing in a narrow stance with eyes open

NEC, COP path while standing in a narrow stance with eyes closed

Table 4. Changes in resting heart rate and blood pressure and peak heart rate and rate of perceived exertion during exercise.

			EX2		EX1		CON	
Variable		Session	X	±SD	X	±SD	X	±SD
Rest	HR	1	10.5	8.58	10.7	8.37	3.5	7.79
		2	9.4	8.89	NA	NA	NA	NA
	SBP	1	-3.6	10.54	-1.9	10.86	-2.5	12.53
		2	-2.6	9.40	NA	NA	NA	NA
	DBP	1	-6.0	10.84	-6.1	11.29	-4.5	12.1
		2	-2.9	10.09	NA	NA	NA	NA
Exercise	HR	1	133.9	7.58	133.6	8.35	126.2	7.53
		2	133.6	7.64	NA	NA	NA	NA
	RPE	1	15.3	1.56	15.2	1.53	9.5	1.58
		2	15.0	1.55	NA	NA	NA	NA

'Session' refers to an intervention session in each group with a morning and an afternoon (i.e., 2) sessions per day in EX2 and one session per day in EX1 and CON.

Values for the top, 'Rest' panel, are post-intervention minus the pre-intervention values averaged across the 25 days

Values for the bottom, 'Exercise' panel, are the average during 25 days of exercise

HR, hear rate, $b \cdot min^{-1}$

SBP and DBP, systolic and diastolic blood pressure, mm·Hg

RPE, rate of perceived exertion

NA, Not applicable because these groups completed one instead two sessions of exercise

The text details the statistical analyses

Table 1. Frequency, medical, and co-morbidity data for 641 stroke participants.

		EX2		EX1		CON		All	
	Sex	X, n	±SD,%	X, n	±SD,%	X, n	±SD,%	X, n	±SD,%
Frequency, n	M	154		149		46		349	
	F	132		123		37		292	
	M, F	286		272		83		641	
Time after	M	2.9	0.74	2.9	0.77	2.8	0.72	2.9	0.75
stroke, weeks	F	2.8	0.74	2.9	0.76	3.1	0.61	2.9	0.74
	M, F	2.8	0.74	2.9	0.77	2.9	0.70	2.9	0.75
RH stroke, n,%	M	25	16	36	24	12	26	73	21
LH stroke, n,%	M	78	51	74	50	22	48	174	50
Cerebellar, n,%	M	42	27	34	23	9	20	85	24
Brainstem, n,%	M	9	6	5	3	3	7	17	5
	All	154	100	149	100	46	100	349	
RH stroke, n,%	F	21	16	22	18	6	16	49	17
LH stroke, n,%	F	70	53	65	53	17	46	152	52
Cerebellar, n,%	F	36	27	27	22	9	24	72	25
Brainstem, n,%	F	5	4	9	7	5	14	19	7
	All	132	100	123	100	37	100	292	100
RH stroke, n,%	M, F	46	16	58	21	18	22	122	19
LH stroke, n,%	M, F	148	52	139	51	39	47	326	51
Cerebellar, n,%	M, F	78	27	61	22	18	22	157	24
Brainstem, n,%	M, F	14	5	14	5	8	10	36	6

	All	286	100	272	100	83	100	641	100
Hypertension,	M	38	25	47	32	21	46	106	30
n, %	F	35	27	19	15	13	35	67	23
	Both	73	26	66	24	34	41	173	27
Ischemic heart	M	31	20	28	19	11	24	70	20
disease, n, %	F	20	15	21	17	12	32	53	18
	Both	51	18	49	18	23	28	123	19
Atherosclerosis,	M	20	13	11	7	5	11	36	10
n, %	F	9	7	17	14	2	5	28	10
	Both	29	10	28	10	7	8	64	10
mRS	F	3.4	0.65	3.3	0.66	3.6	0.61	3.4	0.65
	M	3.4	0.63	3.3	0.67	3.5	0.51	3.4	0.64
	Both	3.4	0.64	3.3	0.67	3.6	0.57	3.4	0.65
Smoking,	M	88	57	79	33	20	43	187	54
n, %	F	74	56	63	51	20	54	157	54
	Both	162	57	142	52	40	48	344	54
Alcohol,	M	53	34	48	32	17	37	118	34
n, %	F	40	30	39	32	9	24	88	30
	Both	93	33	87	32	26	31	206	32

Values in the ‘X, n’ columns denote values as Mean (X) or frequency (n)

Values in the ‘±SD, %’ columns denote values as Standard Deviation or percent

EX2, Two Exergaming sessions daily, 5 days per week for 5 weeks (50 sessions)

EX1, One Exergaming session daily, 5 days per week for 5 weeks (25 sessions)

CON, One standard physical therapy session daily, 5 days per week for 5 weeks (25 sessions)

M, Males

F, Females

RH, right hemisphere

LH, left hemisphere

mRS, Modified Rankin Scale, range: 0 (healthy) to 6 (death)

Alcohol, 1-3 drinks per day

Table 3. Effects of interventions on outcomes.

Variable		EX2 Mean	±SD	EX1 Mean	±SD	CON Mean	±SD	All Mean	±SD	Group	Sex
mRS	M	-1.8	0.79	-1.4	0.94	-0.8	0.74	-1.5	0.92	F=55.3	n.s.
	F	-1.8	0.84	-1.4	0.96	-0.6	0.73	-1.5	0.95	p=0.001	
	Both	-1.8	0.81a	-1.4	0.95	-0.7	0.73	-1.5	0.93	$p\eta^2 = 0.15$	
Mass,	M	-4.8	7.26	-5.5	7.40	-5.2	9.32	-5.2	7.60	F=12.1	127.8
kg	F	-2.0	3.70	1.0	6.08	6.7	8.41	0.4	6.17	p=0.001	0.001
	Both	-3.5	6.05	-2.6	7.56	0.1	10.68	-2.6	7.51	$p\eta^2 = 0.04$	0.17
BI	M	27.0	8.85	19.3	12.22	10.9	7.02	21.6	11.61	F=97.8	n.s.
	F	27.5	9.03	19.0	12.59	9.6	9.01	21.7	12.25	p=0.001	
	Both	27.2	8.92	19.2	12.37	10.3	7.94	21.6	11.9	$p\eta^2=0.24$	
EQ5,	M	9.9	8.47	5.3	8.09	5.4	9.42	7.3	8.72	F=25.6	4.8
mm	F	9.0	9.05	5.0	8.40	1.5	5.88	6.4	8.81	p=0.001	0.028*
	Both	9.5	8.74	5.2	8.22	3.7	8.23	6.9	8.77	$p\eta^2=0.08$	0.00
BBS	M	7.3	6.28	4.7	5.93	2.1	3.53	5.5	6.10	F=32.4	n.s.
	F	6.3	6.25	4.4	6.71	3.7	5.41	5.2	6.42	p=0.001	
	Both	6.8	6.28	4.6	6.29	2.8	4.51	5.3	6.24	$p\eta^2=0.10$	
6MWT,	M	117.3	77.71	108.9	78.74	61.8	60.93	106.4	78.04	F=21.8	n.s.
m	F	132.5	78.10	108.4	68.91	64.0	73.18	113.7	76.72	p=0.001	
	Both	124.3	78.13	108.6	74.32	62.8	66.25	109.7	77.47	$p\eta^2=0.14$	
WEO,	M	-2.4	6.07	-1.2	5.44	-0.1	6.58	-2.5	6.13	F=11.8	n.s.
cm	F	0.4	4.00	-1.4	5.81	-0.4	5.72	-0.5	5.11	p=0.001	

	Both	-1.4	5.75	-1.3	5.60	-0.2	6.17	-1.6	5.77	$p\eta^2$=0.20	
WEC,	M	-4.8	6.84	-1.0	5.70	-1.3	6.06	-2.7	6.53	F=4.1	n.s.
cm	F	-0.4	4.40	-2.4	5.44	-0.2	5.74	-1.2	5.12	p=0.018	
	Both	-2.8	6.23	-1.6	5.62	-0.8	5.91	-2.0	5.97	$p\eta^2$=0.12	
NEO,	M	-3.2	6.33	-1.4	7.45	-0.4	5.88	-2.1	6.84	F=4.4	n.s.
cm	F	-2.5	5.44	-1.4	6.42	-1.5	7.52	-1.9	6.16	p=0.010	
	Both	-2.9	5.93	-1.4	6.99	-0.9	6.64	-2.0	6.53	$p\eta^2$=0.11	
NEC,	M	-3.9	6.84	-1.8	6.64	-1.9	6.67	-2.8	6.79	F=7.2	n.s.
cm	F	-4.5	6.21	-3.0	6.31	-1.6	5.66	-3.5	6.24	p=0.001	
	Both	-4.2	6.55	-2.4	6.51	-1.8	6.21	-3.1	6.55	$p\eta^2$=0.22	

Values are post minus pre mean ±SD change scores in absolute units computed from individual change scores

EX2, Two Exergaming sessions daily, 5 days per week for 5 weeks (50 sessions)

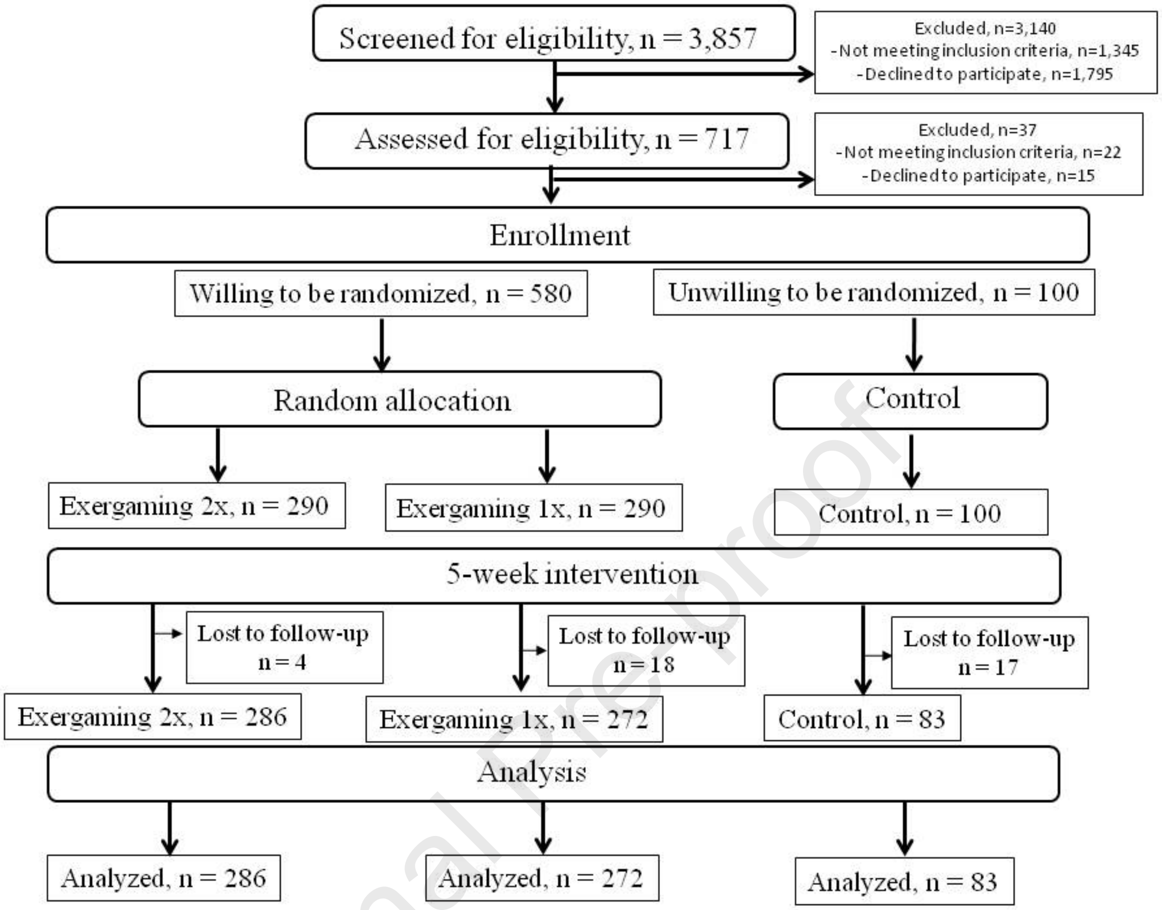
EX1, One Exergaming session daily, 5 days per week for 5 weeks (25 sessions)

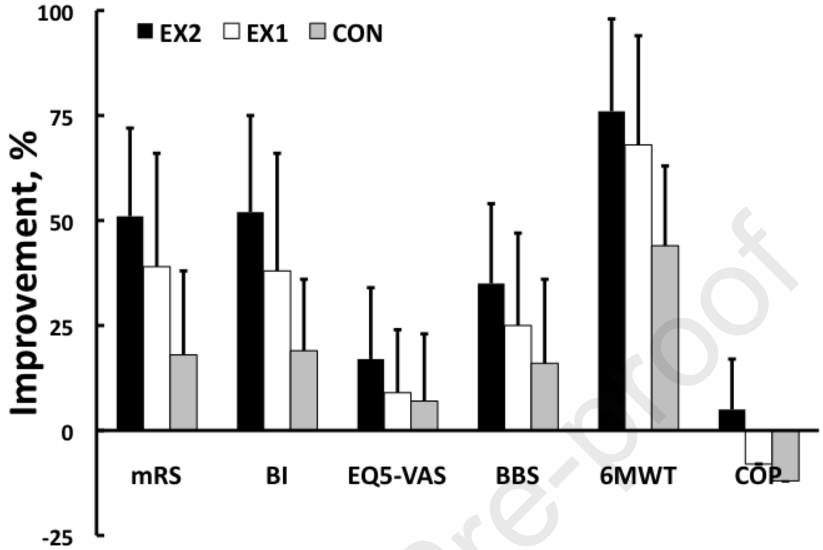
CON, One standard physical therapy session daily, 5 days per week for 5 weeks (25 sessions)

M, Males; F, Females

* Did not survive Holm correction for family wise error (p=0.02 cut-off)

Footnote in Table 2 shows the key to other abbreviations


Screened for eligibility, n = 3,857
Excluded, n=3,140
-Not meeting inclusion criteria, n=1,345
-Declined to participate, n=1,795
Assessed for eligibility, n = 717
Excluded, n=37
-Not meeting inclusion criteria, n=22
-Declined to participate, n=15
Enrollment
Willing to be randomized, n = 580
Unwilling to be randomized, n = 100
Random allocation
Control
Exergaming 2x, n = 290
Exergaming 1x, n = 290
Control, n = 100
5-week intervention
Lost to follow-up n = 4
Lost to follow-up n = 18
Lost to follow-up n = 17
Exergaming 2x, n = 286
Exergaming 1x, n = 272
Control, n = 83
Analysis
Analyzed, n = 286
Analyzed, n = 272
Analyzed, n = 83


EX2
EX1
CON
100
75
50
25
0
-25
Improvement, %
mRS
BI
EQ5-VAS
BBS
6MWT
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