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RESEARCH ARTICLE

Effects of exergaming on exercise capacity in patients with heart failure: results of an international multicentre randomized controlled trial

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Aims Exergaming is a new tool to increase physical activity. This study aimed to determine the effects of access to a home-based exergame (Nintendo Wii) in patients with heart failure (HF) on exercise capacity, self-reported physical activity and patient-reported outcome measures.

Methods and results We enrolled 605 HF patients in New York Heart Association functional class I–IV, independent of ejection fraction, in an international multicentre randomized controlled trial. Patients were randomized to exergame (intervention) or motivational support (control). The primary endpoint was change in submaximal aerobic exercise capacity as measured by the distance walked in 6 min (6MWT) between baseline and 3 months. Secondary endpoints included long-term submaximal aerobic exercise capacity, muscle function, self-reported physical activity, exercise motivation, exercise self-efficacy at 3, 6 and 12 months. At baseline, patients on average walked 403 ± 142 m on the 6MWT. Patients in the exergame group walked further compared to controls at 3 months (454 ± 123 vs. 420 ± 127 m, $P = 0.005$), at 6 months (452 ± 123 vs. 426 ± 133 m, $P = 0.015$) and 12 months (456 ± 122 vs. 420 ± 135 m, $P = 0.004$). However, correcting for baseline 6MWT values by means of a linear mixed-effects model revealed no main effect for the intervention on 6MWT. Small significant effects on muscle function were found. Statistically significant treatment effects were found for muscle function but after correction for baseline and confounders, only the treatment effect for the heel-rise left at 6 months was significant ($P < 0.05$). No treatment effect was found for exercise motivation, exercise self-efficacy, or self-reported physical activity.

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Conclusion Exergaming was safe and feasible in patients with HF with different profiles in different health care systems, cultures and climates. However, it was not effective in improving outcomes on submaximal aerobic exercise capacity. Subgroup analysis did not identify specific subgroups benefiting from the intervention.
Clinical Trial Registration: ClinicalTrial.gov Identifier: NCT01785121.

Keywords Exergaming • Heart failure • Physical activity • Aerobic capacity • Serious Games • Heart failure management

Introduction

According to current guidelines, stable patients with heart failure (HF) should be routinely advised to exercise regularly to improve outcomes.[1–3] However, sedentary lifestyle and low-level daily physical activity in HF patients are very prevalent.[4,5] Adherence has been described as the Achilles' heel of exercise programmes with only 40 to 60% uptake.[5–8] Barriers for physical activity are often related to motivation and self-efficacy (the belief to overcome barriers to physical activity) but also to practical issues, such as time, and travel to rehabilitation centres or even access to a rehabilitation programme.[9–11] In addition, some climates make it difficult for patients to leave their homes to be active. There is a need for evidence-based tailored interventions targeting barriers for physical activity that benefit the individual patient.

Becoming more physically active might be the first step for HF patients to reach the exercise dose needed to improve their health outcomes. A new approach to overcome some of the barriers in reducing sedentary lifestyle is to provide an effective and safe tool at home, which may promote physical activity with no need for the patient to travel or go outdoors. One of these new approaches could be virtual reality gaming. The use of exergames (one of the so-called serious games) is increasingly recognized to have much to offer in the fields of prevention and rehabilitation.[12–15] An exergame is defined as '*the playing of video games that requires rigorous physical exercise, that is intended as a work-out and during which the participant moves large muscle groups in response to cues*'.[14] In these kinds of games, patients can be encouraged to become physically active at their own pace, reducing climate impact and social barriers. Although exergaming has only been tested in two cardiac populations (patients undergoing coronary artery bypass grafting and patients with HF), other studies with older adults have demonstrated higher energy expenditure, improved motor function, better balance and cognitive function, improved quality of life and well-being, a decrease in depressive symptoms, accompanied by a high level of enjoyment along with a feeling of being more connected with family members.[13,15,16] Although not all exergames require 'rigorous' exercise, exergaming can result in more energy expenditure compared to rest and is commonly experienced as light to moderate physical activity in older adults and might therefore be a promising tool to increase physical activity in patients with HF.[13,17] The underlying model of the exergaming and health outcomes is depicted in *Figure 1*.[18]

There have been no studies assessing the effectiveness of exergames in patients with HF and on the motivation to use these games to stay physically active. To avoid a new 'hype' overestimating the effectiveness of these tools, we set out to rigorously test this in a randomized trial. The aim of the present study was to determine the effects of structured access to a home-based exergame (Nintendo Wii sports) in patients with HF on submaximal aerobic exercise capacity and muscle function, exercise motivation and exercise self-efficacy at 3 and also at 6, 12 months. We hypothesized that there will be a significant increase in submaximal aerobic exercise capacity as measured by the 6-min walking test (6MWT) distance between patients who are using an exergame and patients with motivational support only.

Methods

Study design and patients

The HF-Wii study[19] was an open-label randomized study performed in 10 HF centres across three continents. Patients were recruited from five university hospitals, one rehabilitation centre, three regional hospitals, one cardiology outpatient practice, in Sweden, Italy, Israel, the Netherlands, Germany and the USA (in order of study start). Patients were recruited between September 2013 and April 2017.

Eligible participants (>18 years, no upper age limit) had been diagnosed with HF [New York Heart Association (NYHA) class I–IV] by a cardiologist according to European Society of Cardiology (ESC) guidelines[1] (reduced or preserved left ventricular ejection fraction) and spoke the language of the including country.

Patients were excluded if they were unable to use the computer game due to visual impairment (not able to see a TV at 3 m), hearing impairment (not able to telephone), cognitive impairment (assessed by an HF team), motor impairment (not able to swing arm >10 times), or unable to complete questionnaires, having a life expectancy <6 months.

The study was conducted according to the principles of the Declaration of Helsinki (2008) in accordance with the Medical Research Involving Human Subjects Act. In Sweden, ethical approval was obtained centrally (DNR 2012/247-31). Additional approval was obtained from local review boards (NL48647.068.14/METC141085; IT: 0052838/272/UVF/1; IL: 0022-13-RMC; GERS22(a)/2015; USA_UCI IRB HS# 2016-2955). The trial is registered in ClinicalTrials.gov (NCT01785121).

Intervention and control

All patients received regular treatment as well as information about cardiac rehabilitation and physical activity according to standard practice at their referring centre (usual care).

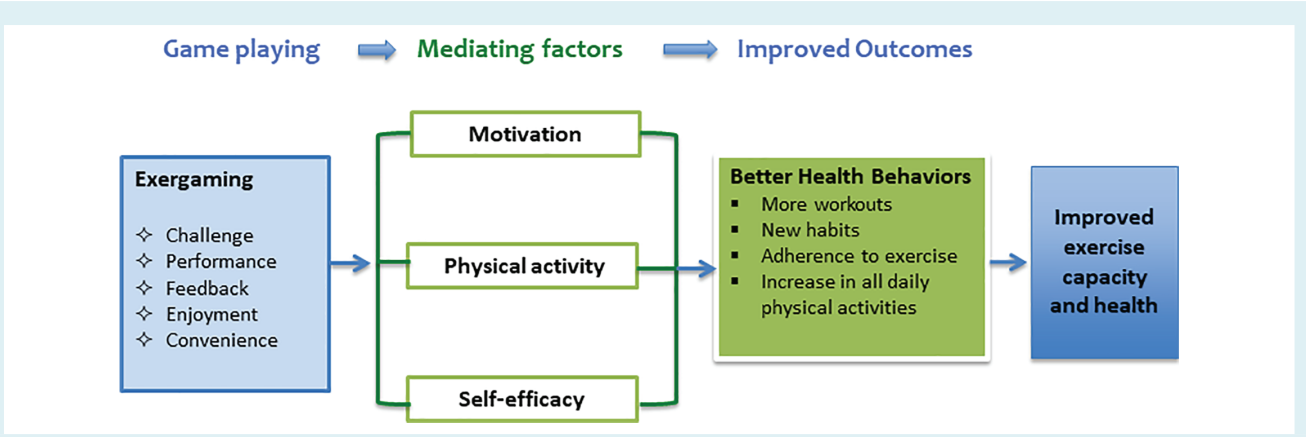

Figure 1 Underlying model of the exergaming and health outcomes.

Intervention group (exergame group)

Patients were introduced to an exergame computer (Nintendo Wii®) in a group-based introduction (2 h) and the exergame was installed at home, receiving also two remote controls and Nintendo Wii Sports with baseball, bowling, boxing, golf, and tennis. They were instructed to move the remote in similar ways the sport is played in real life, e.g. holding and swinging it as a bowling ball. Patients were instructed to exergame 30 min, 5 days a week, adapted to their individual physical condition. For example, if patients were not able to be active for 30 min a day, they were advised to play for as many minutes as possible with an increasing length of time until they reached 30 min a day. Patients were contacted by telephone at 2, 4, 8, and 12 weeks by the instructor following a standard script to discuss frequency of playing or resolve issues with gaming. After 3 months the motivational calls were discontinued. To study effects over time without active support, patients could keep the exergame computer but no additional calls were made.

Control group

Patients received a protocol-based physical activity advice from an HF team member. To balance for extra attention in the intervention group, controls received motivational telephone follow-up at 2, 4, 8, and 12 weeks following a standard script discussing their physical activity.

Procedures

All patients known with stable HF who visited the outpatient HF clinic or admitted with a primary HF diagnosis were evaluated by a local research team member for inclusion and exclusion criteria. Patients received information and once informed consent was signed, patients completed questionnaires and performed the tests during an outpatient clinic visit and were randomized thereafter. All assessments were according to a detailed protocol and were audited for fidelity throughout the study by the same person from the study team. After 3, 6, and 12 months, assessments were performed in the treating clinic. All participants were asked to complete a diary (playing on the exergame computer for the intervention group). Data on adverse events were collected throughout the study and data on mortality were collected from medical records at 12 months.

Randomization and blinding

Randomization was in a 1:1 ratio, stratified by study centre. To achieve balance between study arms and to have similar numbers of patients during the introduction, randomization was done in blocks comprising an equal number of patients (8 or 12) per group. A clinical trial centre (Forum Östergötland) provided a list of computer-generated randomized block allocations for each study centre.

Blinding to treatment allocation for patients was impossible, but outcome assessors of the 6MWT and personnel who entered and checked data were blinded to group assignment.

Study outcomes

The primary endpoint was submaximal aerobic exercise capacity assessed by the 6MWT. The 6MWT (protocol by the American Thoracic Society) is considered a valid method for estimating exercise capacity with predictive power for mortality and morbidity. The walking course was 30 m in length, marked every 3 m, and patients were instructed and encouraged in the same manner in the different centres.

The test has been successfully used for the assessment of many interventions and has strong predictive power for both mortality and morbidity in patients with HF.[20,21]

Secondary outcomes related to physical activity included muscle function, exercise motivation, exercise self-efficacy, and self-reported physical activity.

Muscle function was assessed with unilateral isotonic heel-lift (repetitions), bilateral isometric shoulder abduction (s), unilateral isotonic shoulder flexion (repetitions).[22]

For the unilateral isotonic shoulder flexion, the patients sat comfortably on a stool with their back touching the wall holding a weight (2 kg for women and 3 kg for men) in the hand of the arm to be tested. The pace, 20 contractions per minute, was maintained using a metronome. Patients were asked to elevate one arm, from 0 to 90° flexion, as many times as possible.

For the unilateral isotonic heel-lift, patients performed a maximal heel-lift on a tilted wedge, one lift every other second using a metronome. The contra-lateral foot was held slightly above the floor. The number of maximal heel-rises was counted for each leg. For the bilateral isometric shoulder abduction, patients sat comfortably on a stool with their back touching the wall and with a 1 kg weight in each hand. They were asked to elevate both arms to

shoulder abduction and to maintain this position as long as possible. As the patient tires, the arms automatically start to drop, the assessor instructs the patient to correct the positioning once during the test. The time patients could keep the shoulders in an angle of abduction was recorded. The assessors were trained by the study personnel and supported by video instruction. The tests were performed in a standardized order.

Exercise motivation was assessed by exercise motivation index, measuring exercise motives by 15 statements on a five-point scale from 0–4 (not extremely important).[23]

Self-efficacy was measured with the exercise self-efficacy questionnaire, measuring six potential barriers to exercise scored from 1–10 (not very confident).[24]

Self-reported physical activity was measured by a single item question on the activity of the last week, five answering options were dichotomized to being physically active/inactive less or more than an hour a week.[25]

All adverse events were documented (including orthopaedic events), either reported spontaneously or observed by the local research team.

Data on time exergaming were collected from reports of the telephone calls as part of the intervention and calculated to a 0–100% score. If a subject exceeded the target, the percentage of adherence was recorded as 100%. If the telephone reports from the patient were unclear, the data from the patient diary were used to validate the time exergaming. Clinical data came from medical charts, and if data were not available at the time of inclusion, laboratory tests were accepted if sampled maximally 1 month before inclusion.

Data on the Charlson comorbidity index[26] were collected from the medical chart. Demographic data came from questionnaires collected at baseline, including the Hospital Anxiety and Depression Scale (HADS).[27]

Statistical analysis

The trial was powered to detect a 30 m difference in 6MWT between groups.[19] Based on 80% power, 5% significance, 250 patients in each arm were needed.[21] To ensure appropriate patient numbers at study end, 300 patients per group were planned to be included.

Patient characteristics were reported as numbers (percentages) or means (standard deviation). In line with current recommendations, *P*-values for baseline characteristics were not reported.[28]

Primary and secondary outcomes at follow-up were analysed with a linear mixed model. All models included a residual covariance (GEE type) matrix to correct for repeated measurement in the same patients. All analyses included intervention (vs. control), time and intervention by time interaction. Prior to analyses, normality was examined. Validity of the model (distributional assumptions, homoscedasticity) was assessed with residual analyses.[29]

Prior to analyses, we noted missing values in measurements at baseline and follow-up. Missing values varied between 0.1% and 10.2% for most baseline measurements, except for heel-rise right and left (17.9% and 19.3%, respectively) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (34.0%). To avoid loss of power and potential bias due to missing baseline measurements, we applied multiple imputation for baseline measurements, prognostic factors and confounders. We applied a fully conditional specification with predictive mean matching for continuous variables. Primary and secondary outcomes were not included in the imputation procedure. As missing outcomes may lead to imbalances (and therefore potential bias in treatment effects), we adjusted the planned analysis[19] and performed a mixed model analysis on all follow-up measurements and included a correction for important prognostic factors.[30]

Whereas these earlier documents refer to a change from baseline, we adapted this strategy to correction for baseline (i.e. including the baseline measurements of the corresponding outcome as a covariate) as this optimizes statistical power and corrects for any imbalances already present at baseline.[31]

As planned, first an intention-to-treat analysis was performed followed by a per-protocol analysis. The analysis was performed in three steps. First, only intervention (vs. control), time and intervention by time interaction were included. Second, baseline measurement of the corresponding outcome was included. Third, baseline measurement, known prognostic factors for HF (age, NYHA functional class, log NT-proBNP, HADS) were included. The step 1 models all included a random intercept for centre and an unstructured residual covariance matrix, as this is closely matched to the inclusion and time measurements. For step 2 and step 3 models, almost all models failed to converge. For most outcomes, model convergence was achieved by excluding the random intercept. For some outcomes, we used a simplified residual covariance matrix to achieve convergence. We derived a comparison between the intervention and control groups at follow-up, reported as difference in means with 95% confidence interval (CI) and two-tailed *P*-values.

Per-protocol analyses were performed comparing patients who adhered to the intervention protocol (defined as >80%) to patients in the control group.

In an additional step, we evaluated effect of the intervention on the primary outcome in subgroups of patients. First, we performed likelihood ratio test for corresponding interactions (e.g. treatment by gender and treatment by time by gender). When statistically significant, we subsequently estimated the treatment effect for different subgroups at 3, 6 and 12 months. Treatment interactions with age, gender, NYHA classification, HF with reduced (HFrEF) vs. preserved ejection fraction (HFpEF), depression, anxiety, NT-proBNP, having grandchildren, comorbid stroke, comorbid diabetes and cognitive impairment were tested.

We used a $P < 0.05$ significance level for all statistical tests. Analyses were performed with SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and SPSS v25 (SPSS Inc., Chicago, IL, USA).

Results

Patients

Of 1531 eligible patients, 899 declined, mainly because time, inability to travel, 4% not wanting to use technical equipment.

Participants were younger (67 years) than non-participants (70 years), with no differences in gender distribution. In total, 305 patients were allocated to the exergame group and 300 patients to the control group (*Figure 2*).

Mean age of participants was 67 ± 12 years, predominantly male (71%) and mainly classified as NYHA class II or III. Most patients (72%) were married or living with a partner and 67% had grandchildren. Comorbidities such as diabetes, chronic obstructive pulmonary disease and atrial fibrillation were common. Groups were well balanced regarding baseline characteristics (*Table 1*). Patients were recruited from 10 different centres with the main planned inclusion from the five centres in Sweden (55%) and an equal inclusion from all other centres, except for Germany and

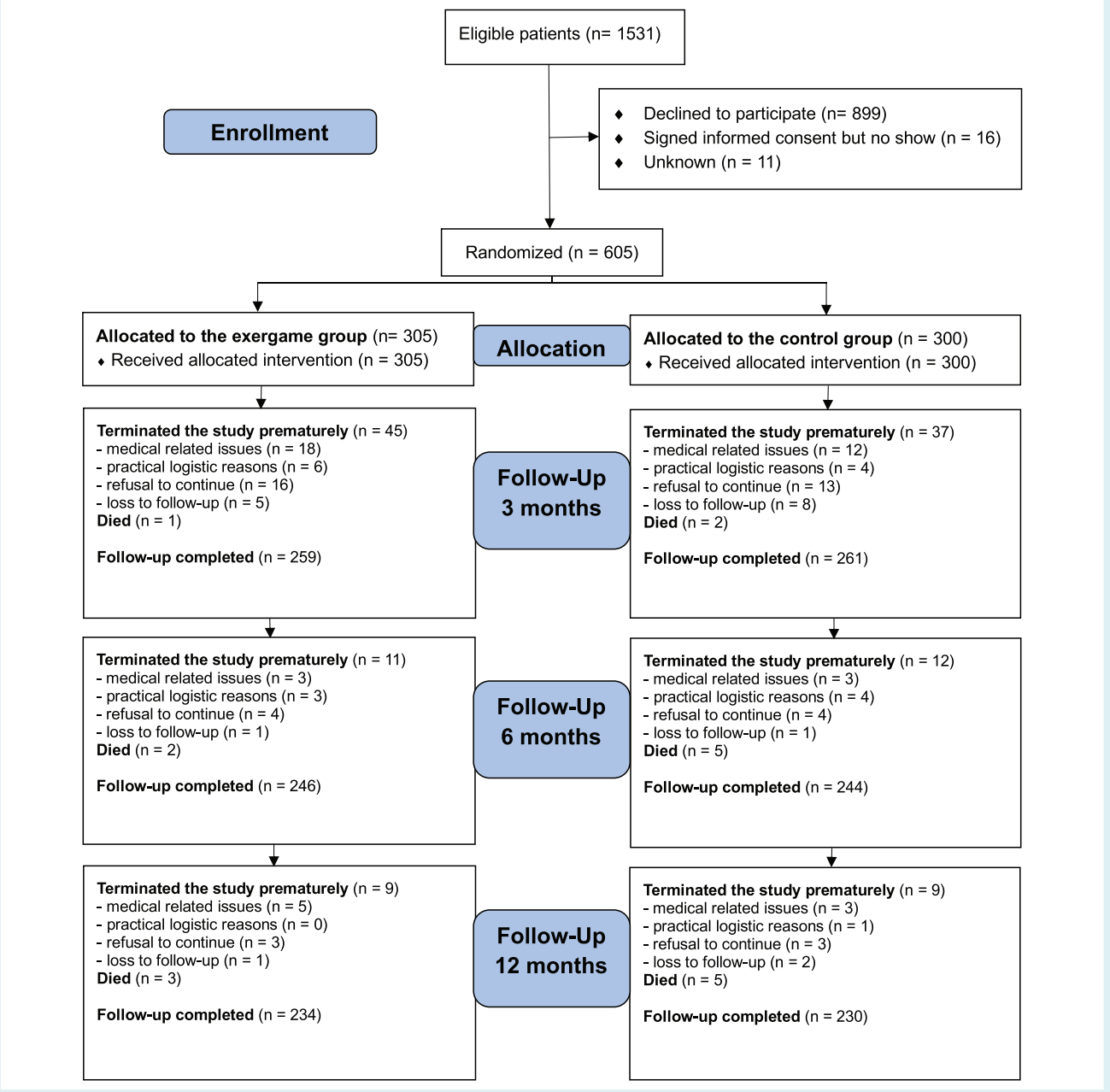

Figure 2 Participant flow in the HF-Wii study.

the US (inclusion of 24 and 8 patients, respectively). Since we used randomization lists for each centre, the distribution between patients in the exergame and control groups was equal within centres.

In total, 18 patients died during the study. No major adverse events were reported related to exergaming. One patient had a cardiac arrest during follow-up 6MWT and was successfully resuscitated.

At 3 months, 82 patients had terminated the study prematurely and, during the remaining months, 41 additional patients discontinued (*Figure 2*).

Regarding adherence to the protocol, 139 patients were > 80% adherent to the recommended playing time whereas 17% reported never having exergamed during the study. Reasons for not exergaming were health deterioration (hospitalization, worsening), events in the family (sickness/death), or practical issues (traveling, other obligations).

Primary endpoint (6-min walk test)

At baseline, patients walked on average 403 ± 142 m on the 6MWT (intervention group: 413 ± 139 m, control 393 ± 144 m).

Table 1 Patient characteristics

	Total (n = 605)	Exergame (n = 305)	Control (n = 300)
Demographics			
Age (years), mean ± SD	67 ± 12	66 ± 12	67 ± 11
Female sex, *n* (%)	175 (29)	85 (28)	90 (30)
Married/living together, *n* (%)	430 (72)	214 (71)	216 (73)
With grandchildren, *n* (%)	402 (67)	196 (65)	206 (69)
Education, *n* (%)			
Low (only primary school)	151 (25)	63 (21)	88 (29)
Medium (high school)	273 (45)	133 (44)	140 (47)
High (university/college)	179 (30)	108 (35)	71 (24)
Clinical profile			
NYHA class, *n* (%)			
I	54 (9)	22 (7)	32 (11)
II	350 (60)	189 (65)	161 (55)
III	171 (30)	80 (27)	91 (32)
IV	4 (1)	2 (1)	2 (1)
LVEF, *n* (%)			
HFrEF	285 (47)	145 (48)	140 (47)
HFmrEF	179 (30)	92 (30)	87 (29)
HFpEF	135 (22)	63 (21)	72 (24)
Aetiology, *n* (%)			
Ischaemic heart disease	249 (42)	130 (44)	119 (41)
Hypertension	260 (44)	128 (43)	132 (45)
Cardiomyopathy	224 (38)	120 (41)	104 (36)
Valvular disease	107 (18)	64 (22)	43 (15)
Body mass index (kg/m^2), mean ± SD	28 ± 5	28 ± 5	28 ± 5
Medication, *n* (%)			
ACE inhibitor/ARB/ARNI	506 (84)	259 (85)	247 (83)
Beta-blocker	522 (87)	263 (87)	259 (88)
MRA	290 (48)	147 (48)	143 (48)
Digoxin	61 (10)	32 (10)	29 (10)
Diuretics	392 (65)	200 (66)	192 (65)
Comorbidity, *n* (%)			
Myocardial infarction	173 (29)	85 (28)	88 (30)
Diabetes	159 (27)	80 (27)	79 (27)
COPD	108 (18)	53 (18)	55 (19)
Stroke	58 (10)	29 (10)	29 (10)
Atrial fibrillation	132 (22)	61 (21)	71 (24)
Devices, *n* (%)			
Pacemaker	104 (18)	46 (15)	58 (20)
CRT	68 (12)	30 (10)	38 (13)
ICD	141 (24)	75 (25)	66 (22)
Time since diagnosis (months), median (IQR)	22 (6–72)	22 (22–66)	23 (7–74)
Laboratory values at baseline, mean ± SD			
Serum sodium (mmol/L)	140 ± 3	140 ± 3	141 ± 3
Serum potassium (mmol/L)	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5
Serum creatinine (μmol/L)	104 ± 42	102 ± 35	106 ± 47
Serum haemoglobin (g/dL)	13.4 ± 1.8	13.5 ± 1.7	13.4 ± 1.8
NT-proBNP (pg/mL), median (IQR)	719 (258–1790)	739 (250–1720)	715 (270–1850)
Symptoms at baseline, mean ± SD			
Dyspnoea (baseline 0–10)	4.67 ± 2.7	4.56 ± 2.7	4.78 ± 2.7
Fatigue (baseline 0–10)	4.77 ± 2.6	4.81 ± 2.5	4.72 ± 2.6
HADS anxiety	5.24 ± 3.8	5.22 ± 3.7	5.26 ± 3.9
HADS depression	5.56 ± 4.2	5.36 ± 4.3	5.76 ± 4.2

ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; HADS, Hospital Anxiety and Depression Scale; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Table 2 Primary and secondary outcomes at baseline and during follow-up

	Exergame	Control
6-min walk test, mean ± SD		
Baseline	413 ± 139 (n = 299)	393 ± 144 (n = 299)
3 months	454 ± 123 (n = 243)	420 ± 127 (n = 243)
6 months	452 ± 123 (n = 215)	426 ± 133 (n = 213)
12 months	456 ± 122 (n = 207)	420 ± 135 (n = 216)
Muscle function tests, mean ± SD		
Heel-rise right (repetitions)		
Baseline	15 ± 9 (n = 255)	14 ± 11 (n = 242)
3 months	16 ± 10 (n = 213)	14 ± 8 (n = 204)
6 months	16 ± 11 (n = 191)	14 ± 10 (n = 181)
12 months	17 ± 11 (n = 176)	15 ± 10 (n = 176)
Heel-rise left (repetitions)		
Baseline	14 ± 9 (n = 248)	14 ± 10 (n = 240)
3 months	15 ± 10 (n = 212)	14 ± 9 (n = 203)
6 months	16 ± 11 (n = 189)	14 ± 9 (n = 179)
12 months	16 ± 10 (n = 169)	15 ± 10 (n = 174)
Bilateral shoulder abduction (s)		
Baseline	85 ± 51 (n = 287)	80 ± 49 (n = 282)
3 months	88 ± 56 (n = 231)	81 ± 47 (n = 231)
6 months	89 ± 52 (n = 210)	83 ± 50 (n = 214)
12 months	84 ± 49 (n = 207)	76 ± 46 (n = 207)
Shoulder flexion right (repetitions)		
Baseline	21 ± 17 (n = 280)	19 ± 14 (n = 285)
3 months	22 ± 13 (n = 233)	21 ± 17 (n = 231)
6 months	23 ± 15 (n = 207)	22 ± 16 (n = 212)
12 months	23 ± 19 (n = 206)	22 ± 16 (n = 208)
Shoulder flexion left (repetitions)		
Baseline	19 ± 12 (n = 283)	18 ± 11 (n = 269)
3 months	21 ± 11 (n = 238)	19 ± 13 (n = 226)
6 months	21 ± 12 (n = 210)	20 ± 14 (206)
12 months	22 ± 13 (n = 212)	20 ± 13 (n = 202)
Exercise motivation (0–4), mean ± SD		
Baseline	2.31 ± 0.88 (n = 282)	2.32 ± 0.87 (n = 283)
3 months	2.17 ± 0.91 (n = 242)	2.18 ± 0.89 (n = 237)
6 months	2.10 ± 0.91 (n = 224)	2.03 ± 0.89 (n = 219)
12 months	2.09 ± 0.87 (n = 215)	2.11 ± 0.91 (n = 216)
Exercise self-efficacy (0–10), mean ± SD		
Baseline	5.10 ± 1.89 (n = 283)	4.93 ± 2.09 (n = 260)
3 months	4.78 ± 1.96 (n = 225)	4.83 ± 2.04 (n = 229)
6 months	4.54 ± 1.90 (n = 215)	4.79 ± 1.98 (n = 214)
12 months	4.54 ± 1.95 (n = 220)	4.56 ± 2.04 (n = 206)
>1 h physically active a week, *n* (%)		
Baseline	184 (61) (n = 301)	201 (68) (n = 260)
3 months	142 (71) (n = 201)	151 (74) (n = 203)
6 months	131 (64) (n = 205)	145 (69) (n = 209)
12 months	125 (61) (n = 204)	129 (64) (n = 201)

SD, standard deviation.

After 3 months, 486 patients completed the 6MWT (*Table 2*). At 3 months, a statistically significant difference in 6MWT was found favouring the exergame group (454 ± 123 m vs. 420 ± 127 m, treatment effect 28.8 m, 95% CI 8.8–48.9; P = 0.005) (*Figure 3*).

The 6MWT distance was longer in the exergame group compared to the control group during follow-up; at 6 months it was 452

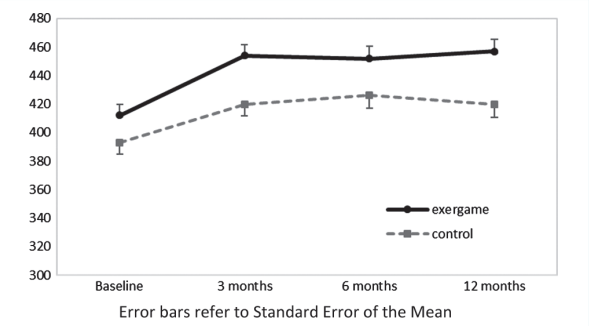

Figure 3 Effects of 6-min walk test (in meters) in the study population.

vs. 426 m (treatment effect 26.3 m, 95% CI 5.1−47.6; $P = 0.015$) and at 12 months it was 456 vs. 420 m (treatment effect 32.2, 95% CI 10.2−54.2; $P = 0.004$) (*Table 3*).

In the exergame group, the mean change in 6MWT (baseline−3 months) was 16 m, 62% improved and 38% decreased distance walked. In controls, this was 15 m, with 62% improving and 38% worsening.

Linear mixed-effects model showed no effect for the intervention on 6MWT after correcting for baseline 6MWT and after correcting for baseline 6MWT and confounders. After correction for baseline, treatment effect decreased to 5.8 m (95% CI −5.5−17.1, $P = 0.317$) at 3 months, to 3.2 m (95% CI −9.3−15.7, $P = 0.612$) at 6 months and to 8.4 m (95% CI −5.9−22.6, $P = 0.249$) at 12 months. After correction for baseline 6MWT and confounders, treatment effect was not statistically significant (*Table 3*).

Muscle function

At baseline, the muscle function values were: heel-rise right 15 ± 10, heel-rise left 14 ± 10, bilateral shoulder abduction 83 ± 50, shoulder flexion right 20 ± 16, shoulder flexion left 19 ± 11. Before correction for the baseline value there was a statistically significant treatment effect at 6 months for heel-rise right with a treatment effect of 2.0 before correction for baseline (95% CI 0.3−3.7, $P = 0.024$) but after correction for baseline values this decreased to 1.4 (95% CI −0.1−3.0, $P = 0.068$). Treatment effect was also statistically significant for heel-rise left after 3 and 6 months, before and after adjustments. At 6 months, the treatment effect was 2.3 (95% CI 0.6−4.0, $P = 0.008$) before correction for baseline, 1.9 (95% CI 0.3−3.5, $P = 0.018$) after correction for baseline, and 1.8 (95% CI 0.2−3.4, $P = 0.026$) after correction for confounders. No treatment effect was found between groups in the other muscle function tests during follow-up, when corrected for baseline values and confounders.

Exercise motivation and exercise self-efficacy

At baseline, patients reported a mean exercise motivation of 2.3 ± 1 and exercise self-efficacy of 5.0 ± 2. No differences were found between groups at follow-up.

Self-reported physical activity

At baseline, 36% of patients reported being physically inactive, and this did not change significantly during follow-up.

Per-protocol analysis

As planned, a per-protocol analysis was performed comparing the 139 patients who adhered to the protocol (≥ 80%) to the 300 controls. Treatment effects on 6MWT and muscle function tests were higher compared to the intention-to-treat, with statistically significant differences in the primary endpoint even after correction for baseline at 3 months, but not at 6 or 12 months or after correction for confounders. Also, larger statically significant effects of treatment were observed on muscle function, specifically on heel-rises (online supplementary *Table S1*).

Subgroup analysis

There was no statistically significant interaction of the intervention with age, gender, NYHA classification, HFrEF/HFpEF, depression, anxiety, NT-proBNP, having grandchildren, comorbid diabetes and cognitive impairment (*Table 4*). Only comorbid history of stroke showed a significant interaction with the treatment effect over time with the likelihood ratio test, showing that patients without a history of stroke improved more as a result of exergaming than patients who had a history of stroke. However, looking at the main effect of the study, exergaming was not strong enough to improve their 6MWT (*Table 5*).

Discussion

The findings of the HF-Wii study showed no statistically significant treatment effect from exergaming on submaximal aerobic exercise capacity. A significant difference in muscle function (heel-rises) was found, but no differences were found related to upper body muscle function, exercise motivation, self-efficacy or self-reported physical activity level. This study evaluated a novel intervention to improve physical activity since it is known that a more active lifestyle is beneficial to patients with HF.

We envisioned that an exergame with active support for 3 months could help patients, irrespective of left ventricular ejection fraction or NYHA class, being physically active and prepare them to reach the optimal exercise dose to improve health outcomes. An earlier pilot study[32] and studies in other populations advocated exergaming as a promising intervention. The ESC guidelines and the consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation[1,10] recommend exercise training for stable NYHA class I−III HF patients and state that early mobilization through an individualized exercise programme may prevent further disability and lay a good foundation for a formal exercise training plan. The aim of the current study was to encourage patients with chronic HF to be more physically active. We did not attempt to provide an exercise training programme, since the intensity would be too low for most patients. Moreover, an exercise programme

Table 3 Comparison of primary and secondary outcomes in the intervention and control groups based on intention-to-treat analysis

	Without correction		With correction for baseline		With correction for baseline and confounders[a]	
	Treatment effect (95% CI)	*P*-value	Treatment effect (95% CI)	*P*-value	Treatment effect (95% CI)	*P*-value
6-min walk test						
3 months	28.8 (8.8–48.9)	0.005	5.8 (−5.5–17.1)	0.317	4.3 (−6.9–15.5)	0.449
6 months	26.3 (5.1–47.6)	0.015	3.2 (−9.3–15.7)	0.612	1.8 (−10.3–14.0)	0.767
12 months	32.2 (10.2–54.2)	0.004	8.4 (−5.9–22.6)	0.249	6.8 (−7.1–20.7)	0.338
Muscle function tests						
Heel-rise right (repetitions)						
3 months	1.4 (−0.1–2.8)	0.063	0.8 (−0.6–2.2)	0.274	0.7 (−0.7–2.1)	0.329
6 months	2.0 (0.3–3.7)	0.024	1.4 (−0.1–2.9)	0.068	1.3 (−0.2–2.9)	0.084
12 months	1.5 (−0.2–3.2)	0.089	0.9 (−0.9–2.7)	0.320	0.9 (−0.9–2.6)	0.348
Heel-rise left (repetitions)						
3 months	1.6 (0.1–3.1)	0.032	1.2 (−0.2–2.6)	0.094	1.1 (−0.3–2.4)	0.137
6 months	2.3 (0.6–4.0)	0.008	1.9 (0.3–3.5)	0.018	1.8 (0.2–3.4)	0.026
12 months	1.1 (−0.5–2.8)	0.174	0.6 (−1.1–2.4)	0.478	0.5 (−1.3–2.3)	0.581
Bilateral shoulder abduction (s)						
3 months	6.7 (−1.3–14.6)	0.100	2.9 (−3.5–9.4)	0.375	2.4 (−4.1–8.8)	0.472
6 months	6.3 (−1.7–14.4)	0.123	2.5 (−4.4–9.4)	0.481	1.9 (−4.9–8.8)	0.579
12 months	9.8 (2.3–17.2)	0.010	6.0 (−0.9–12.8)	0.087	5.4 (−1.4–12.3)	0.121
Shoulder flexion right (repetitions)						
3 months	1.6 (−0.9–4.2)	0.214	0.4 (−1.6–2.4)	0.712	0.0 (−2.0–2.0)	0.979
6 months	1.4 (−1.2–4.1)	0.288	0.2 (−2.1–2.5)	0.847	-0.2 (−2.4–2.1)	0.897
12 months	2.0 (−0.9–4.9)	0.176	0.7 (−1.9–3.3)	0.586	0.3 (−2.3–2.9)	0.800
Shoulder flexion left (repetitions)						
3 months	1.3 (−0.7–3.2)	0.201	0.2 (−1.4–1.9)	0.781	0.0 (−1.6–1.7)	0.974
6 months	1.3 (−0.9–3.5)	0.255	0.4 (−1.5–2.2)	0.712	0.1 (−1.8–2.0)	0.894
12 months	2.7 (0.5–4.9)	0.017	1.7 (−0.1–3.4)	0.065	1.4 (−0.4–3.2)	0.117
Total motivation						
3 months	0.01 (−0.1–0.1)	0.871	−0.02 (−0.1–0.1)	0.765	−0.01 (−0.1–0.1)	0.858
6 months	0.1 (−0.1–0.2)	0.407	0.05 (−0.1–0.2)	0.421	0.1 (−0.1–0.2)	0.360
12 months	−0.002 (−0.1–0.1)	0.979	−0.02 (− 0.1 – 0.1)	0.760	−0.01 (−0.1–0.1)	0.833
Self-efficacy						
3 months	−0.1 (−0.4–0.3)	0.729	−0.1 (−0.4–0.2)	0.597	−0.1 (−0.4–0.2)	0.595
6 months	−0.3 (−0.6–0.1)	0.132	−0.3 (−0.6–0.1)	0.111	−0.3 (−0.6–0.1)	0.120
12 months	−0.1 (−0.4–0.3)	0.765	−0.1 (−0.4–0.3)	0.721	−0.1 (−0.4–0.3)	0.737

CI, confidence interval.
[a]Baseline measurement of outcome, age, New York Heart Association class, N-terminal pro-B-type natriuretic peptide (log), Hospital Anxiety Depression Scale, centre.

is a comprehensive multifaceted intervention which include different modalities (e.g. dynamic, strength, respiratory), and tailored to the individual capacity, all features not applicable to Wii gaming. We envisioned that using exergaming could be a good start to counteract a sedentary habit and to become more physically active. It may promote a tailored activity programme to reach patient expectations and goals.[33]

Although we found a statistically and clinically significant (>30 m) difference in 6MWT between patients in the exergame group and controls, we could not prove a beneficial treatment effect after correction for baseline 6MWT scores.

As in many trials, adherence to the physical activity advice was not 100%. In total, 17% did not exergame despite the introduction lesson and installation at home. Most of the reasons for never playing were related to health deterioration, life events or practical issues, but not because patients did not want to do this kind of activity or did not wish to be active. Per-protocol analysis showed that the effect of exergaming in those adhering was larger both on 6MWT and muscle function tests. For many patients, adherence to physical activity is a challenge[5,10] and introducing them to an exergame might not be a solution for all.[34]

The intensity of exergaming can range from 2.0 to 4.2 METs (bowling vs. boxing).[17] Most patients played bowling and considering that most patients were in NYHA class II–III, this might not have been intensive enough to bring additional value to their daily activities. Future studies on exergaming could consider an entry

Table 4 Subgroup analysis (likelihood ratio test for the primary endpoint (6-min walk test)

Variable	Pooled chi-square	*P*-value
Age	1.33	0.249
Gender	1.94	0.083
NYHA class	1.24	0.241
HFrEF/HFpEF	1.22	0.258
Depression	0.74	0.591
Anxiety	1.08	0.367
NT-proBNP	0.44	0.815
Grandchildren	1.58	0.161
Comorbid stroke	3.96	0.001
Comorbid diabetes	1.80	0.109
Cognitive impairment	0.85	0.597

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

test to target the intensity level and find appropriate games that are close to patients' favourite activities and give coaching and feedback.

We found a small statistically significant treatment effect in muscle function, but it is debatable whether this is clinically relevant.[35] For HF patients who often lose muscle strength, one of the proposed therapeutic strategies is structured resistance exercise.[36] This type of exercise can be tailored to improve endurance in specific activities of daily living.

Future studies that evaluate the effect on exergaming also should consider collecting more clinical and laboratory data, such as changes in blood pressure, blood lipid profile, glycaemic control and waist circumference. Further studies with more specific exergames tailored to improve muscle endurance with continuous repetitive muscle contractions against resistance are therefore needed.

Exergaming did not increase exercise motivation as measured by the questionnaires that included items such as motivation to be physically active in a group. Although patients were encouraged to play the exergame with someone, such as a family member, we did not involve playing in a real-life or virtual group, which could be promising if integrated into exergaming.[34]

We chose to use one specific commercially available exergame for this study since this had the advantages that developmental costs were not needed and that it was easy and attractive to use. To be effective, future games need to be tailored more to specific activity goals and activity levels and to be appealing to cardiac patients with a variety in socio-demographic profiles.

We were able to recruit 605 patients in six different countries with different health care systems and different climate challenges and completion rate of the trial was high. Importantly, no adverse events were detected during exergaming.

The results of the HF-Wii study should be interpreted in the context of some potential limitations. Patients had a relatively low NYHA class compared to the general HF population, a better 6MWT than in other trials (patients walked 403 m compared to 390 m in HF-ACTION[3]) and had high self-reported physical activity,´65% reporting performing moderate activities >1 h/week. This may have resulted in quite 'fit' patients who might not have had enough physical challenge of exergaming. Since no studies were available on testing an exergame in an HF population and we had no indication for the possible best responders to such an intervention, we chose to include the full spectrum of stable HF patients with impaired, mid-range, and preserved ejection fraction as well as the inclusion of the full symptom spectrum from NYHA class I to IV. By applying such broad inclusion, we introduced considerable heterogeneity and possibly might have needed a larger sample size to reach significant effects.

From subgroup analysis we could not identify a subgroup that would clearly benefit from the intervention. However, patients with comorbid stroke gave a small but statistically significant different treatment effect. The concept of exergaming is increasingly tested

Table 5 Treatment effects in subgroup analysis for the primary outcome (6-min walk test) for patients with or without a history of stroke

	Without correction		With correction for baseline		With correction for baseline and confounders[a]	
	Treatment effect (95% CI)	*P*-value	Treatment effect (95% CI)	*P*-value	Treatment effect (95% CI)	*P*-value
With a history of stroke (*n* = 58)						
3 months	−13.1 (−75.6–49.5)	0.681	−9.6 (−44.7–25.4)	0.591	−9.1 (−43.7–25.5)	0.606
6 months	−0.8 (−65.7–64.1)	0.980	4.7 (−32.7–42.1)	0.805	4.5 (−31.9–41.0)	0.807
12 months	−8.2 (−76.2–59.6)	0.810	−5.5 (−49.4–38.3)	0.804	−5.5 (−48.4–37.2)	0.798
No history of stroke (*n* = 547)						
3 months	33.9 (12.7–55.9)	0.002	7.6 (−4.3–19.6)	0.212	5.9 (−5.9–17.7)	0.327
6 months	29.0 (6.8–51.2)	0.01	2.4 (−10.6–15.5)	0.709	0.1 (−11.9–13.5)	0.901
12 months	36.7 (13.6–59.8)	0.002	9.7 (−5.4–24.7)	0.205	8.1 (−6.6–22.7)	0.282

CI, confidence interval.
[a]Corrected for baseline measurement of outcome, age, New York Heart Association class, N-terminal pro-B-type natriuretic peptide (log), Hospital Anxiety Depression Scale.

in stroke patients to improve specific outcomes such as balance or extremity functional recovery. These findings indicate that future researchers should tailor interventions more carefully to relevant comorbid conditions.[37,38]

Furthermore, at 3 months, 119 patients were not able to complete the 6MWT. Although we blinded outcome assessors, blinding of patients was impossible, and we have no data on if controls bought a game computer. We also lacked a pure 'care-as-usual' group, since controls received activity advice, motivational calls and were asked to keep a diary. Although inclusion took place over several years, no large treatment changes were seen in the study population and the treatment was similar in the two study groups. A final limitation is that patients self-reported on time exergaming and the actual time and intensity were not recorded, since such a personal report was not possible with the current device and protocol. We could not interrogate the exergame, since we encouraged people to play with their grandchildren, partner, etc., and they would use the same equipment.

Conclusion

In conclusion, in this first adequately powered trial designed to evaluate the effect of exergaming on exercise capacity in patients with stable HF, we were unable to demonstrate an increase in submaximal aerobic exercise capacity over time. Introducing exergaming was, however, safe and feasible in an HF population involving centres with different patient profiles in diverse health care systems and climates. We performed retrospective subgroup analysis and were unable to define any specific subgroups benefiting from the intervention. Other interventions involving exergaming specifically targeted at this (older) group of HF patients and with better adherence might prove to be more effective.

Clinical perspectives

Introducing exergaming is safe and feasible in an HF population involving centres with different patient profiles in diverse health care systems and climates. Advising an exergame to patient with HF cannot replace other physical activity advice or rehabilitation programmes. Additional adaptation is needed to be effective to improve exercise capacity.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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