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ORIGINAL RESEARCH ARTICLE

Factors associated with lack of improvement in submaximal exercise capacity of patients with heart failure

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Abstract

Aims Improvement in exercise capacity is the primary goal of physical activity programmes for patients with heart failure (HF). Although activity programmes are effective for some patients, others do not benefit. Identifying factors related to a lack of improvement in submaximal exercise capacity may help us interpret findings and design new interventions. The aim of this study is to identify factors contributing to a lack of improvement in submaximal exercise capacity 3 months after physical activity advice or an exergame intervention in patients with HF. Additionally, we aimed to assess differences in lack of improvement in submaximal exercise capacity of patients whose baseline exercise capacity predicted a worse compared with better prognosis of HF.

Methods and results This secondary analysis of the HF-Wii study analysed baseline and 3 month data of the 6 min walk test (6MWT) from 480 patients (mean age 67 years, 72% male). Data were analysed separately in patients with a pre-defined 6 min walking distance at baseline of <300 m (n = 79) and ≥300 m (n = 401). Among patients with a baseline 6MWT of ≥300 m, 18% had deteriorated submaximal exercise capacity. In the multiple logistic regression analysis, lower baseline levels of self-reported physical activity [odds ratio (OR) = 0.77, 95% confidence interval (CI) = 0.60–0.97], lower baseline levels of cognitive function (OR = 0.87, 95%CI = 0.79–0.96) were significantly associated with lack of improvement in exercise capacity at 3 months. Not randomized to exergaming (OR = 0.63, 95%CI = 0.37–1.09) was likely (P = 0.097) to be associated with lack of improvement in exercise capacity at 3 months. Among the 79 patients with baseline 6MWT of <300 m, 41% (n = 32) did not improve 6MWT distance at 3 months. Independent predictors for the lack of improvement for 6MWT were New York Heart Association class III/IV (OR = 4.68, 95%CI = 1.08–20.35), higher levels of serum creatinine (OR = 1.02, 95%CI = 1.003–1.03), lower cognitive function (OR = 0.86, 95%CI = 0.75–0.99), and fewer anxiety symptoms (OR = 0.84, 95%CI = 0.72–0.98).

Conclusions Lower self-reported physical activity and cognitive impairment predict lack of improvement in submaximal exercise capacity in HF patients. Patients who have a worse prognosis (score <300 m at the 6MWT) are often frail and gain less in exercise capacity. These patients may need a more comprehensive approach to have an effect on exercise capacity, including an individually tailored exercise programme with aerobic exercise (if tolerated) and strength exercises.

Keywords Heart failure; 6 min walk test; Submaximal exercise capacity; Physical activity

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Introduction

Physical activity and exercise are essential for patients with heart failure (HF) to improve functional capacity, quality of life, and prognosis.[1–3] It is recommended that patients with HF should be physically active daily and activities should be adapted to symptoms and personal preferences.[4] However, several factors may hinder patients from being as physically active as they would wish to be, such as symptoms of breathlessness, fatigue, or lack of sport facilities.[2,5] As HF is a progressive disease, it can be expected that a constant adaptation of physical activity is needed during the HF trajectory. If improvement cannot be realized, even maintaining a stable level of physical activity is valuable.

The 6 min walk test (6MWT) is a low-cost and reliable method for estimating submaximal exercise capacity; only a 30 m pre-measured level surface and a timing device are needed.[6] The distance walked on the 6MWT is correlated with exercise duration and oxygen uptake at peak exercise and is used to assess interventions or determine subgroups of patients that might benefit from certain interventions.[7–9] The 6MWT has been shown to have a strong predictive power for both mortality and morbidity in patients with HF.[10–12] In a study of 1714 patients with HF, a decline in 6MWT was found to be associated with a worse prognosis and not modified by treatment up-titration.[7] A threshold of 300 m at the 6MWT is associated with a worse (<300 m) and a better (≥300 m) prognosis in HF patients[11,12] and a meaningful improvement in submaximal exercise capacity is previously defined as a change of more than 30 m.[13] An increase of 30 to 50 m in 6MWT distance over time is previously considered a clinically significant improvement and found to be associated with a significant improvement in New York Heart Association functional class (NYHA) and health-related quality of life.[14–16]

In the HF-Wii study,[17] we tested the effect of an exergame intervention to improve physical activity in submaximal exercise capacity as measured by the 6MWT and compared it with a control group of patients whom only received physical activity advice. Although one-third of the patients improved submaximal exercise capacity during follow-up, many patients did not improve or even deteriorated in the 6MWT, both in the intervention and the control groups.

To understand further this lack of effect and to design optimally tailored physical activity interventions for the future, we aimed to identify factors related to lack of improvement and deterioration of submaximal exercise capacity 3 months after an exergame intervention or physical activity advice in patients with HF. Additionally, we aimed to assess differences in lack of improvement in submaximal exercise capacity of patients whose baseline exercise capacity predicted a worse (<300 m) vs. a better (≥300 m) prognosis.

Methods

Study design and participants

This study is a secondary data analysis from an international randomized controlled intervention study, the HF-Wii study, performed at 10 HF centres in Sweden, Italy, the Netherlands, Israel, Germany, and the United States, with recruitment between 2013 and 2017.[17,18] Eligible participants (>18 years, no upper age limit) had been diagnosed with HF (NYHA class I–IV) independent of ejection fraction and spoke the language of the including country. Patients were excluded if they could not use the exergame due to visual, hearing, cognitive, or motor impairment, were unable to complete questionnaires or had a life expectancy < 6 months.

Patients were randomized to exergame (intervention) or physical activity advice (control). In the intervention group, the patients were instructed to exergame 30 min per 5 days a week, adapted to their physical condition. Patients were contacted by telephone after 2, 4, 8, and 12 weeks to discuss the frequency of playing or solve possible technical problems with the exergame platform. In the control group, patients received advice from medical staff in the HF team. They received telephone follow-up calls after 2, 4, 8, and 12 weeks to discuss their current physical activity.

The study was conducted according to the Declaration of Helsinki (2008) principles following the Medical Research Involving Human Subjects Act. In Sweden, ethical approval was obtained centrally (DNR 2012/247-31), and additional approval was obtained from the local medical ethics committees (the Netherlands NL48647.068.14/METC141085; Italy 0052838/272/U.V.F/1 (2014); Israel 0022-13-RMC; Germany S22(a)/2015; USA UCI IRB HS# 2016-2955). The trial is registered in ClinicalTrials.gov (NCT01785121).[17]

Measurements

Submaximal exercise capacity

To examine changes in submaximal exercise capacity at patient level, differences between the 6MWT at baseline and after 3 months were calculated per patient.[10]

According to the 2002 statement of the American Thoracic Society, the self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test.[19]

As prior studies have shown that a threshold of 300 m at the 6MWT is associated with a worse (<300 m) and a better (≥300 m) prognosis in HF patients,[11] we divided patients into two groups: those who scored <300 m at the 6MWT at baseline and those who scored ≥300 m. Moreover, considering that a meaningful improvement in submaximal exercise capacity was defined as a change of >30 m from the baseline distance walked in the 6MWT,[13] it is possible to formulate two assumptions:

1 if a patient has a relatively low baseline distance of 6MWT (<300 m), a positive outcome is a meaningful improvement of ≥30 m. A lack of improvement is defined as a difference of less than 30 m between baseline and follow-up.
2 if a patient had a relatively high baseline 6MWT distance (≥300 m), 6MWT distance should at least stay at the same level and not decline >30 m. So, for patients with a baseline 6MWT distance ≥300 m, a lack of improvement is defined as a decrease over time of more than 30 m.

Shortness of breath and fatigue were assessed with a numeric rating scale ranging from no experience of fatigue or shortness of breath (0) to worst experienced fatigue or shortness of breath (10).

Cognitive impairment was assessed with the Montreal Cognitive Assessment (MoCA), which is a brief screening instrument to detect mild cognitive impairment.[20] The MoCA scores range between 0 and 30. Higher MoCA scores indicate better cognitive function. A score of 26–30 is considered normal; 18–25 is considered a mild cognitive impairment, 10–17 is a moderate cognitive impairment, and less than 10 is considered a severe cognitive impairment.[20,21]

Depression and anxiety were measured with the Hospital Anxiety and Depression Scale, consisting of 14 items (response scale 0–3), which are divided into two subscales of 7 items, each measuring anxiety and depression.[22] Each scale has a score between 0 and 21), with a score ≥7 indicating the presence of depression and anxiety.[22]

Exercise motivation was assessed by the Exercise Motivation Index, measuring exercise motivation using 15 statements on a 5-point scale from 0 (*not important*) to 4 (*extremely important*).[23]

Self-efficacy was measured with the Exercise Self-Efficacy questionnaire, which measures the extent to which an individual feels confident to exercise despite six potential barriers. Possible scores range from 1 (*not very confident*) to 10 (*very confident*).[24]

Self-reported physical activity was measured with a single-item question regarding the activity of the last week, with five answering options (1 = no activity, 2 = less than 30 min/week, 3 = 30–60 min/week, 4 = more than 1 to 3 h/week, 5 = more than 3 h a week).[25]

The following *demographic and clinical variables* of patients were collected from the questionnaires and medical records: age, gender, marital status, education, NYHA classification, aetiology of HF, duration of HF, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, pulse rate, blood pressure, serum haemoglobin, creatinine, body mass index, comorbidities, medications, and smoking status.

Statistical analysis

In all analyses, patients either from the intervention or the control groups were analysed as one group because we aimed to identify factors related to the lack of improvement in submaximal exercise capacity at 3 months, independent of allocated groups. However, in the analysis, we corrected for group assignment. Categorical data are presented as frequencies and percentages. For continuous variables with a normal distribution, the mean and standard deviations are reported. For variables not normally distributed, the median and interquartile ranges are reported. Student's *t*-test was used to compare normally distributed continuous data, and Mann–Whitney *U*-test was used for non-normally distributed continuous data. Categorical variables were compared with the χ^2 test or Fisher's exact test as appropriate.

To identify factors associated with a lack of improvement, three multiple logistic regression analyses were performed. Variables associated with a lack of improvement in univariate analysis ($P < 0.015$) were entered in the multivariate model and then selected using the backward selection method. Baseline 6MWT and group assignment were forcedly entered into the multivariate model.

Missing self-administered questionnaires were not replaced in the present analysis because there were only a few patients who had a few missing items in each instrument (approximately 0.006% to 0.04%) and, in most other cases, patients did not answer any items (0.01–0.02%).

All statistical tests were two-tailed, and statistical significance was defined as $P < 0.05$. All analyses were performed with SAS version 9.4 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

Results

Of the 605 patients included in the HF-Wii study, 82 patients terminated the study prematurely, mostly due to medically related issues or refusal to continue, and three patients died.[17] Of a total of 520 patients who were included in the 3 month follow-up, 40 patients had no complete values for the 6MWT at baseline and/or the 3 month follow-up. For this secondary analysis, we used data of the 480 patients in the HF-Wii study who had completed a 6MWT both at baseline and at the 3 month follow-up. The mean age of the patients included in the present study was 67 years, and approximately 30% were female, 64% were classified as NYHA II (*Table 1*). There were no significant differences between the 145 patients that terminated the study prematurely or did not complete the 6MWT and the 480 patients included in the analysis concerning age, sex, and NYHA class.

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Table 1 Baseline characteristics of the sample (N = 480)

	All (N = 480)	6MWT distance at baseline < 300 m (n = 79)	6MWT distance at baseline ≥ 300 m (n = 401)	P value
6MWT distance (m)				
At baseline	421.0 ± 131.3	195.9 ± 70.5	465.4 ± 87.8	<0.001
At 3 months	436.5 ± 126.5	256.1 ± 93.6	472.0 ± 98.9	<0.001
Absolute changes in 6MWT (m)	15.5 ± 65.9	60.2 ± 86.4	6.7 ± 57.2	<0.001
Improved, 30 m < change	160 (33%)	47 (59%)	113 (28%)	<0.001
Equal, −30 ≤ change ≤ 30 m	239 (50%)	24 (30%)	215 (54%)	
Deterioration, change < −30 m	81 (17%)	8 (10%)	73 (18%)	
Relative changes in 6MWT distance, %, median (Q1–Q3)	3.3 (−3.5–11.7)	25.4 (3.2–69.2)	2.4 (−4.5–8.0)	<0.001
Group, exergame	238 (50%)	32 (41%)	206 (51%)	0.078
Age (years)	66.7 ± 11.3	73.3 ± 9.3	65.4 ± 11.3	<0.001
Gender, female	134 (28%)	109 (27%)	109 (27%)	0.419
Married/living together	351 (74%)	50 (63%)	301 (76%)	0.023
With grandchildren	322 (68%)	66 (84%)	256 (65%)	0.001
Education				0.003
Low (compulsory school)	117 (25%)	31 (39%)	86 (24%)	
Medium (upper secondary education)	218 (45%)	29 (37%)	189 (47%)	
High (university/college)	145 (30%)	19 (24%)	126 (31%)	
NYHA functional classification				
I	45 (9.8%)	2 (2.6%)	43 (11%)	<0.001
II	294 (64%)	33 (43%)	261(68%)	
III	119 (26%)	41(54%)	78 (20%)	
Ischemic aetiology of HF	197 (42%)	28 (36%)	169 (43%)	0.225
Duration of HF (months)	20 (6–72)	12 (2–72)	23 (7–72)	0.056
LVEF dysfunction				0.006
Normal	96 (20%)	24 (31%)	72 (18%)	
Mild	144 (30%)	28 (35%)	116 (29%)	
Moderate to severe	237 (50%)	27 (34%)	210 (53%)	
NT pro-BNP, pg/mL median, (Q1–Q3)	681 (250–1790)	2247 (942–4127)	620 (244–1552)	<0.001
Pulse rate (beat/min)	69.7 ± 12.1	73.3 ± 11.2	68.9 ± 12.2	0.001
Systolic BP (mmHg)	123.4 ± 17.8	122.2 ± 19.0	123.7 ± 17.6	0.502
Diastolic BP (mmHg)	72.3 ± 11.5	69.8 ± 9.8	72.8 ± 11.8	0.020
Serum haemoglobin (g/dL)	13.5 ± 1.7	12.4 ± 1.9	13.7 ± 1.6	<0.001
Serum creatinine (μmol/L)	101.2 ± 36.1	107.3 ± 50.5	100.0 ± 32.5	0.229
Body mass index (kg/m^2)	27.9 ± 4.8	27.2 ± 5.7	28.0 ± 4.6	0.235
Comorbidity				
Cerebrovascular disease	48 (10%)	10 (13%)	38 (9.7%)	0.423
Diabetes	116 (25%)	28 (35%)	88 (22%)	0.014
COPD	76 (16%)	26 (33%)	50 (13%)	<0.001
Cancer	49 (10%)	6 (7.6%)	43 (11%)	0.370
Medical therapy				
ACEI and/or ARB	418 (87%)	48 (61%)	370 (93%)	<0.001
Beta-blocker	423 (89%)	55 (70%)	368 (93%)	<0.001
MRA	237 (50%)	30 (38%)	207 (52%)	0.023
CRT	54 (11%)	9 (12%)	45 (11%)	0.916
ICD	118 (25%)	13 (17%)	105 (27%)	0.079
Current smoker	37 (7.1%)	7 (8.9%)	27 (6.8%)	0.512
Heart failure symptoms				
Short of breath score	4.5 ± 2.6	3.9 ± 3.1	4.6 ± 2.5	0.070
Fatigue score	4.6 ± 2.6	5.0 ± 2.8	4.6 ± 2.5	0.201
Cognitive impairment				
MoCA score	24.7 ± 3.4	21.9 ± 4.2	25.3 ± 3.0	<0.001
No or light	163 (34%)	10 (13%)	153 (39%)	<0.001
Mild	292 (62%)	54 (68%)	238 (60%)	
Moderate	19 (4.0%)	15 (19%)	4 (1.0%)	
Depression	102 (22%)	30 (39%)	72 (18%)	<0.001
HADS depression score	4.9 ± 3.6	7.0 ± 4.0	4.5 ± 3.4	<0.001
Anxiety	139 (29%)	36 (47%)	103 (26%)	<0.001
HADS anxiety score	5.4 ± 4.0	6.9 ± 4.6	5.1 ± 3.8	<0.001
Motivation score	2.3 ± 0.9	2.7 ± 0.9	2.2 ± 0.8	<0.001
Self-efficacy score	5.1 ± 2.0	4.3 ± 1.9	5.3 ± 1.9	0.001
Physical activity	3.8 ± 1.2	3.7 ± 1.5	3.8 ± 1.2	0.369
1, No activity	36 (7.6%)	12 (15%)	24(6.1%)	0.031
2, <30 min/week	37 (7.8%)	6 (7.6%)	31(7.8%)	
3, 30–60 min/week	84 (18%)	10 (13%)	74 (19%)	
4, <1 h ≤ 3 h/week	141 (30%)	18 (23%)	123 (31%)	
5, >3 h/week	178 (37%)	33 (42%)	145 (37%)	

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HADS, hospital anxiety and depression scale; ICD, implantable cardioverter defibrillator; MoCA, Montreal Cognitive Assessment; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association.

Eighty-four per cent of the patients (*n* = 401) had a baseline 6MWT distance of ≥300 m, and 36 patients walked more than 600 m during the baseline test. In total, 16% of the patients (*n* = 79) walked less than 300 m, with seven patients having a baseline 6MWT distance of fewer than 100 m. Compared with patients with a baseline 6MWT distance of ≥300 m, patients with a 6MWT distance of <300 m were significantly older (65 vs. 73 years), had higher NYHA class (NYHA ≥ III, 20% vs. 54%), had more mild or moderate cognitive impairment (61% vs. 87%), and had more comorbidities such as diabetes (22% vs. 35%), chronic obstructive pulmonary disease (13% vs. 33%), and depression (18% vs. 39%) (*Table 1*).

Factors related to lack of improvement in submaximal exercise capacity across the total group

The mean change of the 6MWT between baseline and at 3 months in the entire group was an increase of 15.5 ± 65.9 m. In total, 33% of the patients (*n* = 160) improved more than 30 m at 3 months, 50% (*n* = 239) had no clinically significant change (≤30 m), and 17% (*n* = 81) deteriorated in distance walked on the 6MWT by more than 30 m. *Table 2* shows the results of univariate analysis after correcting for baseline distance of 6MWT. A multivariate analysis adjusted for baseline 6MWT and group assignment showed that lower levels of self-reported physical activity [odds ratio (OR) = 0.81, 95% confidence interval (CI) = 0.65–0.997)] and lower cognitive function (OR = 0.87, 95%CI = 0.80–0.94) were independent predictors of lack of improvement in submaximal exercise capacity at 3 months in all study patients. Not being in the exergame group was likely to be associated with a lack of improvement (OR = 0.63, 95%CI = 0.37–1.09, *P* = 0.097).

Factors related to lack of improvement in submaximal exercise capacity according to baseline 6MWT distance (<300 and ≥300 m)

Among the 79 patients with a 6MWT distance of <300 m at baseline, 59% of the patients (*n* = 47) improved the distance walked at 3 months, 41% (*n* = 32) did not improve their distance. The mean change in distance of 6MWT between baseline and 3 months was an increase of 60.2 ± 86.4 m. Results of univariate analysis after the baseline correction of 6MWT are shown in *Table 2*. In the multivariate analysis, independent predictors for the lack of improvement for 6MWT were NYHA III/IV (OR = 4.68, 95%CI = 1.08–20.35), higher levels of serum creatinine (OR = 1.02, 95%CI = 1.003–1.03), lower cognitive function (OR = 0.86, 95%CI = 0.75–0.99), and fewer anxiety symptoms (OR = 0.84, 95%CI = 0.72–0.98).

Among the 401 patients with a higher baseline 6MWT distance of ≥300 m, the mean changes in the distance of 6MWT increased by 6.7 ± 57.2 m. Eighteen per cent of the patients (*n* = 73) deteriorated more than 30 m in 6MWT distance at 3 months, 28% (*n* = 113) improved, and 54% (*n* = 215) stayed the same. Lower levels of physical activity (OR = 0.77, 95%CI = 0.60–0.97) and lower cognitive function (OR = 0.87, 95%CI = 0.79–0.96) were significantly associated with lack of improvement for 6MWT. Not being in the exergame group was likely to be associated with a lack of improvement only in the patients with a baseline 6MWT distance of ≥300 m *Table*s 3 and 4.

Discussion

Our findings showed that lower self-reported physical activity and cognitive impairment were predictors of lack of improvement in submaximal exercise capacity in patients. However, when we analysed data from patients who scored <300 and ≥300 m on the 6MWT, we identified different predictors of lack of improvement in submaximal exercise capacity. Lack of improvement was specifically associated with higher NYHA class, higher creatinine, worse cognitive impairment, and lower anxiety in patients who walked <300 m at the 6MWT, and lower self-reported physical activity and worse cognitive impairment in those who walked ≥300 m in the 6MWT. To our knowledge, no prior studies have analysed predictors of lack of improvement in exercise capacity separately.

Two important messages can be derived from this study in which we analysed the change of submaximal exercise capacity in 480 patients with HF enrolled in an activity trial. The first main message is to consider the complex nature of change in exercise capacity in a sample of patients with considerable comorbidity and different exercise capacity levels before an intervention, who have challenges with cognition and psychosocial issues. Second, it is vital to reflect on the optimal use of 6MWT as an endpoint of activity trials in HF patients.

In this study, in patients who scored <300 m at the 6MWT at baseline, lack of improvement in exercise capacity was predicted by higher NYHA class, higher creatinine, worse cognitive impairment, and lower anxiety. Several of these factors are also considered in the definition of frailty in patients with HF, in which four domains are recognized: clinical (e.g. comorbidities), psycho-cognitive (e.g. cognitive impairment), functional (e.g. low mobility), and social (poor/no social support).[26] The prevalence of frailty is around 40% in patients with HF.[27] Several factors included in the above four domains can be addressed with interventions to improve outcomes, and exercise capacity is one variable. Trials focused on improving exercise capacity in frail HF patients are scarce,

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Table 2 Factors related to lack of improvement in submaximal exercise capacity in all patients (N = 480)

	Univariate analysis after baseline correction of 6MWT				Multivariate analysis			
		95%CI				95%CI		
	OR	Lower	Upper	P value	OR	Lower	Upper	P value
Baseline 6MWT distance	1.002	1.000	1.004	0.045	1.01	1.002	1.01	<0.001
Randomization, Wii	0.73	0.44	1.004	0.218	0.63	0.37	1.09	0.097
Age	1.02	0.99	1.04	0.211				
Gender, female	1.14	0.66	1.97	1.648				
Married/living together	1.03	0.58	1.83	0.913				
Grandchildren	0.72	0.41	1.25	0.244				
Education, ≥University	1.09	0.64	1.86	0.752				
NYHA class, III/IV	1.89	1.00	3.56	0.050				
Ischemic aetiology	1.48	0.88	2.52	0.142				
Duration of HF, ≥2 years	0.98	0.58	1.66	0.949				
LVEF dysfunction	0.97	0.69	1.34	0.835				
Pulse rate (beat/min)	1.02	1.002	1.04	0.034				
Systolic BP (mmHg)	1.002	0.99	1.02	0.770				
Diastolic BP (mmHg)	1.003	0.98	1.03	0.769				
Body mass index	0.98	0.93	1.04	0.576				
Comorbidity, yes								
Stroke	0.90	0.39	2.11	0.813				
Diabetes	1.11	0.62	1.98	0.734				
Renal disease	1.23	0.48	3.14	0.664				
COPD	1.33	0.67	2.66	0.412				
Cancer	0.89	0.38	2.08	0.791				
Therapy, yes								
ACEI/ARB	0.83	0.37	1.88	0.662				
Beta-blocker	0.63	0.29	1.36	0.239				
MRA	1.19	0.72	1.95	0.505				
CRT	1.21	0.58	2.53	0.619				
ICD	0.63	0.34	1.17	0.145				
Serum haemoglobin (g/dL)	0.96	0.81	1.12	0.586				
Serum creatinine, μmol/L	1.00	0.99	1.01	0.945				
Current smoker	1.30	0.51	3.30	0.586				
Heart failure symptoms								
Short of breath score	1.00	0.91	1.10	0.976				
Fatigue score	0.99	0.90	1.10	0.896				
Physical activity self-reported	0.83	0.68	1.02	0.073	0.81	0.65	0.997	0.047
MoCA cognitive score	0.88	0.81	0.95	0.001	0.87	0.80	0.94	0.001
HADS depression score	0.99	0.92	1.07	0.824				
HADS anxiety score	1.03	0.96	1.09	0.433				
Motivation score	1.33	0.97	1.82	0.076				
Self-efficacy score	1.11	0.97	1.28	0.133				

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HADS, hospital anxiety and depression scale; ICD, implantable cardioverter defibrillator; MoCA, Montreal Cognitive Assessment; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; OR, odds ratio.
Dependent variable: change of 6MWT distance between baseline and 3 months < -30 m.

but a recent study[28] demonstrated that exercise capacity in frail HF patients could achieve a greater improvement with high-intensity training.

The second lesson from this study is that using the 6MWT as an endpoint is valuable but should be considered with its limitations. Although the 6MWT has been used in previous HF studies to measure exercise capacity[28] and can measure changes over time, ceiling effects can occur. In patients with preserved exercise capacity, the ceiling effect may be a limitation to consider the lack of improvement. Our study had 36 patients who walked more than 600 m in the 6MWT during the baseline test, and probably, this group of patients is not expected to increase a score that has been reported in healthy adults in prior studies (range from 400 to 700 m).[29] In a study of patients with pulmonary arterial hypertension, a ceiling effect was found, and it was difficult to determine the changes in walking distance in patients with a baseline 6MWT higher than 450 m.[16] The 6MWT is often used to substitute the cardiorespiratory assessment of peak oxygen consumption in a maximal symptom-limited exercise and not specifically to measure physical activity. The 6MWT might perform better in patients with severe and symptomatic HF, whose 6MWT is most severely limited and an improvement could be clinically meaningful.[12] However, at the same time, we found that 40% of patients who had a relatively low 6MWT at baseline, and in whom one expects an increase

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Table 3 Predictors for lack of improvement and decline after baseline correction according to 6 min walk distance at baseline: univariate analysis

	6MWT < 300 m (*n* = 81)				6MWT ≥ 300 m (*n* = 401)			
	6MWT changes of ≤30 m				6MWT change of ≤30 m			
		95%CI				95%CI		
Lack of improvement	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
Baseline 6MWT distance	1.01	0.999	1.01	0.117	1.002	0.999	1.005	0.236
Randomization, Wii	0.97	0.37	2.40	0.942	0.71	0.42	1.22	0.223
Age	1.08	1.01	1.14	0.016	1.01	0.98	1.04	0.490
Gender, female	1.87	0.66	5.31	0.242	1.19	0.67	2.14	0.551
Married/living together	0.72	0.27	1.91	0.505	0.96	0.52	1.76	0.894
Grandchildren	0.64	0.17	2.34	0.497	0.79	0.44	1.40	0.412
Education, ≥University	0.54	0.17	1.76	0.307	1.16	0.67	2.02	0.600
NYHA class, III/IV	3.68	1.16	11.72	0.027	1.68	0.84	3.36	0.146
Ischemic aetiology	2.02	0.74	5.52	0.168	1.58	0.90	2.78	0.110
Duration of HF, ≥2 years	2.03	0.74	5.57	0.169	0.95	0.54	1.68	0.868
LVEF dysfunction	0.88	0.49	1.59	0.674	0.94	0.66	1.34	0.730
Pulse rate (beat/min)	0.99	0.95	1.03	0.525	1.02	0.999	1.04	0.061
Systolic BP (mmHg)	1.001	0.98	1.03	0.930	1.002	0.99	1.02	0.776
Diastolic BP (mmHg)	1.02	0.97	1.07	0.420	1.01	0.98	1.03	0.685
Body mass index	1.05	0.97	1.15	0.223	0.97	0.92	1.03	0.370
Comorbidity								
Stroke	2.30	0.58	9.19	0.238	0.90	0.36	2.25	0.817
Diabetes	1.16	0.45	3.04	0.758	1.10	0.59	2.07	0.758
Renal disease	1.39	0.44	4.39	0.578	1.58	0.55	4.49	0.395
COPD	1.73	0.63	4.80	0.289	1.14	0.52	2.52	0.739
Cancer	0.63	0.10	3.79	0.613	0.83	0.33	2.07	0.690
Medical therapy								
ACEI/ARB	1.14	0.44	2.96	0.782	0.72	0.27	1.88	0.499
Beta-blocker	0.63	0.23	1.73	0.370	0.71	0.28	1.86	0.490
MRA	1.08	0.42	2.81	0.874	1.13	0.66	1.92	0.661
CRT	2.06	0.50	8.51	0.319	1.03	0.45	2.33	0.947
ICD	1.36	0.40	4.57	0.625	0.55	0.28	1.08	0.080
Serum haemoglobin (g/dL)	0.98	0.76	1.25	0.840	1.00	0.84	1.19	0.975
Serum creatinine (μmol/L)	1.01	1.003	1.03	0.009	0.999	0.99	1.01	0.750
Current smoker	—				1.57	0.60	4.14	0.359
Heart failure symptoms								
Short of breath score	1.03	0.88	1.19	0.745	1.002	0.90	1.12	0.974
Fatigue score	1.02	0.85	1.21	0.874	0.99	0.89	1.11	0.902
Physical activity	0.94	0.68	1.30	0.703	0.79	0.63	0.98	0.035
MoCA cognitive score	0.87	0.77	0.99	0.030	0.87	0.80	0.95	0.002
HADS depression score	0.98	0.87	1.10	0.705	1.002	0.93	1.08	0.954
HADS anxiety score	0.91	0.81	1.01	0.092	1.05	0.98	1.13	0.137
Motivation score	1.42	0.84	2.41	0.191	1.32	0.94	1.85	0.111
Self-efficacy score	1.08	0.83	1.42	0.556	1.03	0.89	1.20	0.685
EHFScBS self-care score	0.99	0.97	1.01	0.393	0.99	0.98	1.01	0.178

6MWT, distance in 6 min walk test; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HADS, hospital anxiety and depression scale; ICD, implantable cardioverter defibrillator; MoCA, Montreal Cognitive Assessment; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; OR, odds ratio.
Higher MoCA scores indicate better cognitive function. LVEF dysfunction (1 = normal, 2 = mild, 3 = moderate to severe)

after an activity intervention, did not improve submaximal exercise capacity. In this group in which all patients had a relatively low baseline level, even their baseline 6MWT was independently associated with lack of improvement. This strong association with the baseline might indicate that these patients might be so symptomatic or suffer from comorbidity that a rather low intensity intervention might not be enough for them to improve their submaximal exercise capacity significantly.

Finally, we found that not being in the exergame group was likely to be associated with a lack of improvement only in the patients with a baseline 6MWT distance of ≥300 m. In the main study, we did not find a significant effect of exergaming in the total sample,[17] but the current results confirm that future efforts should be made to tailor interventions to patients who are most susceptible to change. Exergaming might be suitable for some, while other patients might benefit from more conventional exercise programmes, such as walking, training in a gym, and hydrotherapy.

The present study has clinical relevance by studying an activity intervention in an international group of patients with HF and provides insight into factors related to change in

Table 4 Independent predictors for lack of improvement according to the 6 min walk distance at baseline in a multivariate logistic regression analysis

	6MWT < 300 m (n = 72)				6MWT ≥ 300 m (n = 345)			
	Equal or deterioration 6MWT changes of <30 m				Deterioration 6MWT change of < −30 m			
		95%CI				95%CI		
Lack of improvement	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
Baseline 6MWT distance	1.01	1.000	1.02	0.043	1.01	1.002	1.01	0.004
Randomization, Wii	1.05	0.31	3.56	0.941	0.61	0.34	1.09	0.092
NYHA class, III/IV	4.68	1.08	20.35	0.040	—			
Serum creatinine (μmol/L)	1.02	1.003	1.03	0.014	—			
Physical activity	—				0.77	0.60	0.97	0.029
MoCA cognitive score	0.86	0.75	0.99	0.048	0.87	0.79	0.96	0.003
HADS anxiety score	0.84	0.72	0.98	0.031	—			

6MWT, distance in 6 min walk test; CI, confidence interval; HADS, hospital anxiety and depression scale; MoCA, Montreal Cognitive Assessment; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; OR, odds ratio.
Physical activity (1 = no activity, 2 = less than 30 min/week, 3 = 30–60 min/week, 4 = more than 1 h up till 3 h/week, 5 = more than 3 h a week). Higher MoCA scores indicate better cognitive function. Higher HADS anxiety scores indicate having more anxiety symptoms.

submaximal exercise capacity of patients who received an exercise intervention. The threshold of 300 m of the 6MWT can be used to tailor interventions. According to this study, as well as others,[30] the patients who walked <300 m at the 6MWT are more likely to be frail. They may need a more comprehensive intervention to influence exercise capacity, including an individually tailored exercise programme with aerobic exercise (if tolerated) and strength exercises. Other aspects such as adequate treatment of comorbidities and depression and social support might be included. This study is limited by being a secondary analysis. Furthermore, a total of 6.6% of patients did not have complete values of the 6MWT at baseline and/or 3 month follow-up, mostly due to physical impairments. Patients who could not perform the 6MWT at baseline probably had a 6MWT lower than 300 m, and patients that could not perform the 6MWT at follow-up had most likely a decline in 6MWT.

Conclusions and clinical implications

Lack of improvement in submaximal exercise capacity in HF patients was associated with lower self-reported physical activity and cognitive impairment. These findings are important because they may help health care professionals to identify non-responding patients with HF suitable for participation in interventions aimed at improving physical activity (advice and exergame in our HF-Wii study). Patients with a worse prognosis (score <300 m at the 6MWT), who may be defined as frail, gained less in exercise capacity. These patients may need a more comprehensive approach to have an effect on exercise capacity, including an individually tailored exercise programme, with aerobic exercise (if tolerated) and strength exercises, for example, an individually adapted and coached exercise programme.

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Conflict of interest

The authors declare that they have no conflict of interest.

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