ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 812–821
Published online 30 December 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13781

ORIGINAL ARTICLE

Brisk walking can be a maximal effort in heart failure patients: a comparison of cardiopulmonary exercise and 6 min walking test cardiorespiratory data

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Abstract

Aims Cardiopulmonary exercise test (CPET) and 6 min walking test (6MWT) are frequently used in heart failure (HF). CPET is a maximal exercise, whereas 6MWT is a self-selected constant load test usually considered a submaximal, and therefore safer, exercise, but this has not been tested previously. The aim of this study was to compare the cardiorespiratory parameters collected during CPET and 6MWT in a large group of healthy subjects and patients with HF of different severity.

Methods and results Subjects performed a standard maximal CPET and a 6MWT wearing a portable device allowing breath-by-breath measurement of cardiorespiratory parameters. HF patients were grouped according to their CPET peak oxygen uptake (peak$\dot{V}O_2$). One hundred and fifty-five subjects were enrolled, of whom 40 were healthy (59 ± 8 years; male 67%) and 115 were HF patients (69 ± 10 years; male 80%; left ventricular ejection fraction 34.6 ± 12.0%). CPET peak$\dot{V}O_2$ was 13.5 ± 3.5 mL/kg/min in HF patients and 28.1 ± 7.4 mL/kg/min in healthy subjects ($P < 0.001$). 6MWT-$\dot{V}O_2$ was 98 ± 20% of the CPET peak$\dot{V}O_2$ values in HF patients, while 72 ± 20% in healthy subjects ($P < 0.001$). 6MWT-$\dot{V}O_2$ was >110% of CPET peak$\dot{V}O_2$ in 42% of more severe HF patients (peak$\dot{V}O_2 < 12$ mL/kg/min). Similar results have been found for ventilation and heart rate. Of note, the slope of the relationship between $\dot{V}O_2$ at 6MWT, reported as a percentage of CPET peak$\dot{V}O_2$ vs. 6MWT $\dot{V}O_2$ reported as the absolute value, progressively increased as exercise limitation did.

Conclusions In conclusion, the last minute of 6MWT must be perceived as a maximal or even supramaximal exercise activity in patients with more severe HF. Our findings should influence the safety procedures needed for the 6MWT in HF.

Keywords Heart failure; Exercise; 6 min walking test; Dyspnoea; Oxygen consumption

Received: 1 September 2021; Revised: 25 October 2021; Accepted: 13 December 2021
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Introduction

Cardiopulmonary exercise testing (CPET) is the gold standard method for measuring exercise performance, usually reported as peak oxygen uptake (peak $\dot{V}O_2$). CPET is applied in different populations including healthy subjects, athletes, and patients with various pathological conditions such as heart failure (HF).[1,2] In all these settings, CPET provides relevant information on top of exercise performance and prognosis as regards cardiac, respiratory, and muscle function and limitations.[3] However, CPET limited availability as well as the need for trained staff for test supervision and data interpretation make it not accessible as desirable in every setting. Therefore, in clinical practice and in research trials or in large cohort studies, it is common to assess exercise performance and prognosis by simpler tests such as the 6 min walking test (6MWT).

There are conflicting data regarding the extent to which 6MWT represents a metabolically maximal test and about the correlation between peak $\dot{V}O_2$ and the distance walked at 6MWT.[4–7] Maximal CPET and 6MWT are in fact two different tests: CPET is a maximal exercise, usually performed with a progressive increase of workload (ramp protocol) aimed at achieving a maximal effort in 8–12 min,[8] whereas 6MWT is a constant load test and it is usually considered a submaximal, and therefore believed safer, exercise. Specifically, it is commonly perceived that in more severe patients, a maximal test such as CPET carries a higher risk than a submaximal exercise (e.g. 6MWT). This is confirmed by the discrepancy between the safety measures normally required to perform the two tests (e.g. presence of trained personnel, defibrillator, electrocardiogram monitoring, and presence of a stretcher to handle emergencies).[1,9]

The aim of this study is to compare CPET cardiorespiratory parameters with those collected with a portable metabolimeter during 6MWT in a large group of healthy subjects and patients with HF of different severity.

Materials and methods

Anonymized data and materials will be made publicly available at https://zenodo.org/.

One hundred and fifteen HF patients and 40 healthy volunteers participated in the study. Healthy subjects (age 18–80 years) were recruited through word of mouth among hospital employees and their relatives and friends. We excluded athletes or subjects engaged in an intense training programme. All underwent medical history collection and full clinical evaluation including electrocardiogram. None was on treatment with any drugs possibly affecting the cardiorespiratory system. HF patients were recruited at Heart Failure Units of Centro Cardiologico Monzino, IRCCS, and Istituti Clinici Scientifici Maugeri, IRCCS. In all study locations, subjects underwent the same exercise protocol and data analysis, for both CPET and 6MWT. Patients were clinically stable with no recent admissions for worsening HF. Inclusion criteria were as follows: age 18–80 years and New York Heart Association I–III. As part of our routine HF assessment, all patients underwent at least one previous CPET and 6MWT at our laboratory, which confirmed that patients were familiar with the procedures and setting.[10,11] Exclusion criteria were the use of long-term oxygen therapy, previous heart transplantation or left ventricular assist device, neuromuscular co-morbidities affecting the possibility to perform both exercise tests, and concomitant moderate or more severe chronic obstructive pulmonary disease.[12] The presence of a permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy was not exclusion criteria. However, we excluded pacemaker-dependent patients with device-induced heart rate (HR).

All patients were on optimal medical therapy with standard HF medications at the highest tolerated dose.

The protocol complies with the World Medical Association Declaration of Helsinki, and it was approved by the Ethics Committee of Centro Cardiologico Monzino, IRCCS, Milan (MEC08-3-032), and of Istituti Clinici Scientifici Maugeri, IRCCS (CE 2204). Informed consent was obtained from all subjects. Data collection was prospective.

All HF patients were evaluated by left ventricular ejection fraction (LVEF) (Simpson biplane method) by cardiac ultrasound[13] and underwent N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP) measurements. BNP values were converted in NT-proBNP equivalent using 6.25 as correction factor (n = 35).[14]

Cardiopulmonary exercise test

Cardiopulmonary exercise tests were usually performed in the early afternoon. All CPETs were performed by means of a stationary ergospirometer (Quark PFT, COSMED, Rome, Italy) using an electronically braked cycle ergometer. The progressively increasing workload exercise protocol (ramp) was set to achieve peak exercise in ~10 min.[8] In the absence of clinical events, CPET was interrupted when the subjects stated that they had reached maximal effort. We performed a breath-by-breath analysis of expiratory gases and ventilation ($\dot{V}_E$). $\dot{V}_E$ vs. carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) slope was calculated as the slope of the linear relationship between $\dot{V}_E$ and $\dot{V}CO_2$ from 1 min after the beginning of the loaded exercise to the end of the isocapnic buffering period.[3] The respiratory exchange ratio (RER) was measured as $\dot{V}CO_2/\dot{V}O_2$, and we use 1.05 as a cut-off value to define a maximal exercise.[15] CPETs were conducted on a different day from 6MWT.

Six-minute walking test

The 6MWTs were performed between one and two working days from the CPET and at the same time of the day of CPET using a dedicated hospital corridor. The metabolic values during the 6MWT were collected and assessed using a wearable ergospirometer (K5, COSMED).[16] As per standard procedure, the K5 ergospirometer was calibrated every day following factory instructions.[17,18] Breath-by-breath measurements of $\dot{V}O_2$, $\dot{V}_E$, and $\dot{V}CO_2$ were recorded while the subjects were performing exercises.[16,18] HR was monitored through an HR monitor (Polar T31, Polar Electro Oy, Kempele, Finland).

Moreover, all participants were asked to score the degree of fatigue at the beginning and at the end of the exercise using a modified Borg symptom score ranging from 0 (no symptoms) to 10 (worst symptoms) points.[19]

We performed a standard 6MWT in all participants collecting the usual parameters (total distance walked measured in metres, Borg scale, HR, and haemoglobin oxygen saturation (SpO_2) at the beginning and at the end of the 6MWT)[9] on top of cardiorespiratory parameters. We instructed subjects to walk at regular pace as far as they could from end to end during the test. Every 60 s, subjects were encouraged with a standard sentence also mentioning the elapsed time.[9]

Figure 1 shows a subject performing the 6MWT with the K5 equipment (upper panel) and an example of breath-by-breath data collected ($\dot{V}O_2$ and $\dot{V}_E$).

K5 wearable ergospirometer has been extensively used and validated.[17,18]

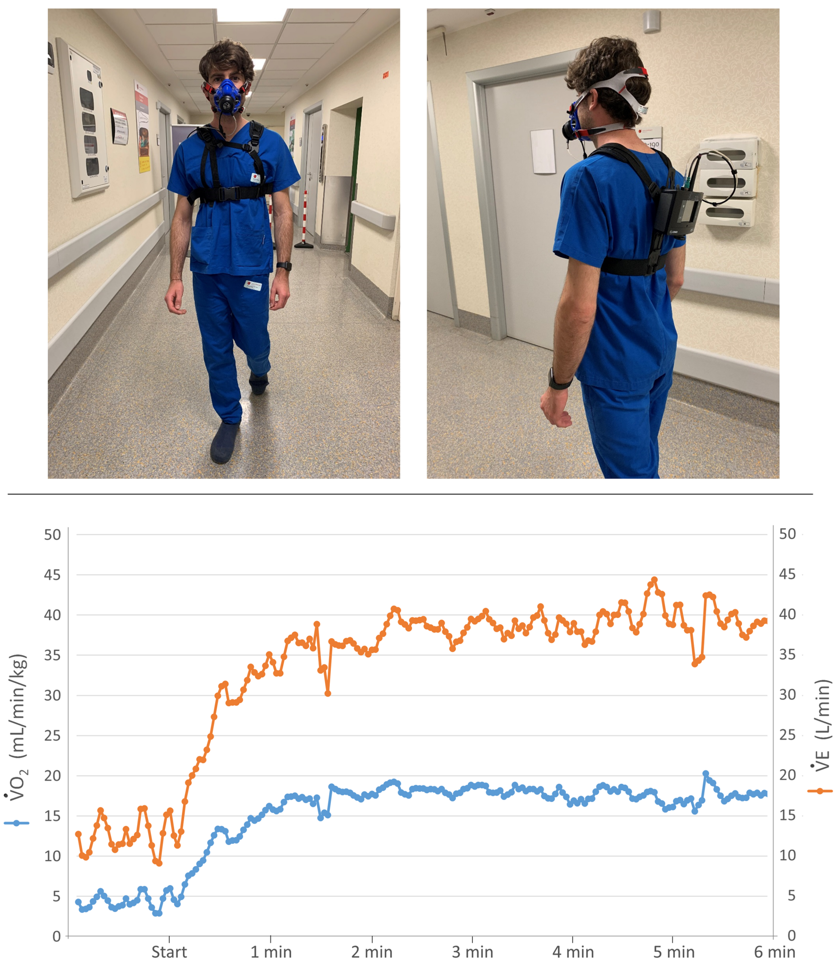
Statistical analysis

Cardiopulmonary exercise test data are reported as average over 20 s or slopes as appropriate.[3] As proposed by Wasserman *et al.*,[20] patients were divided into three groups according to peak $\dot{V}O_2$: <12, 12–16, and >16 mL/kg/min.

Oxygen uptake during 6MWT (6MWT-$\dot{V}O_2$) was calculated and expressed both as mL/kg/min and as a per cent of the peak $\dot{V}O_2$ obtained at CPET. 6MWT cardiorespiratory parameters are the average of the last 60 s of exercise.

Data were recorded breath by breath. To account for erratic breaths, we cleaned outliers as follows: data were removed if they deviated above the 75th percentile or below the 25th percentile more than two times the 25–75th percentile delta. The analysis was performed within each test; considering all 6MWTs, the breaths removed for $\dot{V}O_2$ were 1.90% of the recorded breaths. A similar percentage of breaths were removed for the other analysed variables.

Figure 1 Example of a subject performing a 6 min walking test wearing a portable metabolimeter (K5, COSMED, Rome, Italy) (upper panel). In the lower panel are shown oxygen uptake ($\dot{V}O_2$) and ventilation ($\dot{V}_E$) traces of the same subject during a complete 6 min walking test.



Normally distributed data, expressed as mean ± standard deviation, were examined by Student's *t*-test to compare patients and controls. For non-normally distributed parameters, data are expressed as the median and inter-quartile range. Trends across severity groups were assessed by analysis of covariance.

The associations between 6MWT and CPET parameters were evaluated with linear regression.

Analyses were carried out with the SAS statistical package v. 9.4 (SAS Institute Inc., Cary, NC, USA), and all tests were two sided. $P < 0.05$ was considered statistically significant.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

A total number of 155 subjects were enrolled (66 ± 11 years; male 77%), of whom 40 were healthy (59 ± 8 years; male 67%, body mass index 25.1 ± 3.4 kg/m^2) and 115 were HF patients (69 ± 10 years; male 80%, body mass index 26.2 ± 4.3 kg/m^2; $P < 0.01$ for age and gender distribution vs. healthy subjects). One healthy subject and nine patients were active smokers.

Heart failure patients had an average LVEF of 34.6 ± 12.0% and a median NT-proBNP of 1994 pg/mL [733–5329]. Specifically, 27 patients (23%) had an LVEF > 40% (HF with preserved or middle range ejection fraction), and 88 (77%) had HF with reduced LVEF. Beta-blocker therapy was present in 105 patients (91%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 66 (57%), angiotensin receptor–neprilysin inhibitor in 40 (35%), mineralocorticoid antagonist in 69 (60%), diuretic in 104 (90%), anticoagulants in 36 (31%), antiplatelet agents in 29 (25%), and digitalis in 6 (5%). Healthy subjects were not taking any medication.

Both CPET and 6MWT were performed without untoward events in all cases. *Table 1* shows cardiopulmonary variables at CPET and at 6MWT of HF and healthy subjects. HF patients were stratified by peak $\dot{V}O_2$: Group 1, <12 mL/kg/min (*n* = 45); Group 2, 12–16 mL/kg/min (*n* = 44); and Group 3, >16 mL/kg/min (*n* = 26). Groups characteristics were as follows: (i) Group 1, 71.5 ± 9.4 years, female gender 10 (22%), LVEF 34.5 ± 12.7%, NT-proBNP 3262 [1196–8799], and 91% of patients received beta-blockers; (ii) Group 2, 69.5 ± 7.4 years, female gender 8 (18%), LVEF 33.3 ± 12.1%, NT-proBNP 1668 [618–3821], and 91% of patients received

Table 1 Metabolic data during cardiopulmonary exercise test and during 6 min walking test in healthy subjects and heart failure patients

	Healthy subjects (*n* = 40)			Patients (*n* = 115)			
	n	Mean	SD	*n*	Mean	SD	*P*
Cardiopulmonary exercise test							
Peak $\dot{V}O_2$ (mL/min)	40	2047	581	115	1008	296	<0.001
Peak $\dot{V}O_2$ (mL/kg/min)	40	28.1	7.4	115	13.5	3.5	<0.001
$\dot{V}_E/\dot{V}CO_2$ slope	40	27.2	4.0	115	37.8	9.4	<0.001
Peak VE (L/min)	40	81.1	23.1	115	47.1	13.3	<0.001
Peak RER	40	1.18	0.10	115	1.09	0.12	<0.001
$\dot{V}O_2$/work	40	10.1	1.1	92	8.5	1.7	<0.001
Rest HR (b.p.m.)	35	74	11	113	64	9	<0.001
Peak HR (b.p.m.)	40	154	16	116	100	24	<0.001
Peak work (W)	40	172	53	115	78	26	<0.001
6 min walking test							
Basal $\dot{V}O_2$ 6MWT (L/min)	40	428	97	115	508	140	0.001
$\dot{V}O_2$ 6MWT (L/min)	40	1410	317	115	959	270	<0.001
$\dot{V}O_2$ 6MWT (mL/kg/min)	40	19.4	3.9	115	12.8	3.2	<0.001
$\dot{V}O_2$ 6MWT (% peak $\dot{V}O_2$)	40	72%	20%	114	98%	20%	<0.001
$\dot{V}_E$ 6MWT (L/min)	40	36.1	8.8	115	33.1	9.4	0.079
VT 6MWT (L)	40	1.5	0.4	114	1.2	0.3	<0.001
$\dot{V}_E/\dot{V}CO_2$ 6MWT	40	32.0	3.1	115	45.0	7.8	<0.001
Basal HR 6MWH (b.p.m.)	40	80.9	15.1	114	69.9	10.7	<0.001
HR 6MWT (b.p.m.)	40	108.3	19.0	115	87.2	16.7	<0.001
$PetO_2$ 6MWT (mmHg)	40	104.9	3.6	115	111.1	5.4	<0.001
$PetCO_2$ 6MWT(mmHg)	40	39.0	3.0	114	30.6	4.4	<0.001
$\dot{V}CO_2$ 6MWT (mL/min)	40	1140	262	115	753	214	<0.001
RER 6MWT	40	1.03	0.06	115	1.07	0.14	0.014
Distance 6MWT (m)	40	498	55	114	390	90	<0.001
SpO_2 basal 6MWT (%)	40	97.9	0.9	113	97.1	1.5	0.001
SpO_2 stop 6MWT (%)	40	97.1	1.4	113	96.1	2.7	0.025
Borg scale	40	2 [1–3.25]		115	3 [1–4.8]		0.094

6MWT, 6 min walking test; HR, heart rate; Peak, peak exercise at cardiopulmonary exercise test; $PetCO_2$, end-tidal carbon dioxide pressure; $PetO_2$, end-tidal oxygen pressure; RER, respiratory gas exchange; SpO_2, haemoglobin oxygen saturation; $\dot{V}CO_2$, expired CO_2 volume; $\dot{V}_E$, ventilation; $\dot{V}O_2$, oxygen uptake; VT, tidal volume.

beta-blockers; and (iii) Group 3, 62.2 ± 13 years, female gender 5 (19%), LVEF 35.6 ± 10.6%, NT-proBNP 1994 [729–5607], and 96% of patients received beta-blockers. According to exercise limitation severity, patients showed higher $\dot{V}_E/\dot{V}CO_2$ slope and lower peak workload and $\dot{V}O_2$/work values (*Table 2*).

The correlation between peak $\dot{V}O_2$ at CPET and 6MWT-$\dot{V}O_2$ expressed as a per cent of the CPET peak $\dot{V}O_2$ (6MWT-$\dot{V}O_2$%) is shown in *Figure 2A*. The 6MWT-$\dot{V}O_2$% was 98 ± 20% and 72 ± 20% in HF and healthy subjects, respectively ($P < 0.001$; *Table 1*). Specifically, 1 healthy and 27 HF subjects had a 6MWT-$\dot{V}O_2$ > 110% of the peak $\dot{V}O_2$, as shown in *Figure 2B*. *Figure 2C* shows the correlation between peak $\dot{V}_E$ and 6MWT-$\dot{V}_E$ expressed as the % of peak $\dot{V}_E$ at CPET (6MWT-$\dot{V}_E$ %), while in *Figure 2E*, we reported the correlation between peak HR and 6MWT-HR as % of peak HR at CPET (6MWT-HR%). The respective proportion of subjects who exceeded the 100% of HR and $\dot{V}_E$ values obtained at CPET is reported in *Figure 2D* and *2F*, respectively.

Figure 3 shows a correlation between peak $\dot{V}O_2$ (upper panel) or 6MWT-$\dot{V}O_2$ (lower panel) and distance walked during 6MWT in the entire study population. Moreover, the $\dot{V}O_2$ reached at the two tests showed a good correlation both in the whole population ($r = 0.736$, $P < 0.001$) and considering only HF patients ($r = 0.584$, $P < 0.001$). 6MWT-$\dot{V}O_2$ significantly correlates with 6MWT-$\dot{V}O_2$% in HF patients ($r = 0.427$, $P < 0.001$) and in healthy subjects ($r = 0.406$, $P < 0.01$), while it does not if the whole population is considered, including healthy subjects ($r = -0.016$, P = ns). Specifically, the slope of the 6MWT-$\dot{V}O_2$% vs. 6MWT-$\dot{V}O_2$ relationship progressively increased as exercise limitation did (*Figure 4*).

Regarding 6MWT results, the greater the exercise limitation severity, the lower were absolute 6MWT-$\dot{V}O_2$ values, paralleled by a progressive increase in 6MWT-$\dot{V}O_2$% and $\dot{V}_E/\dot{V}CO_2$ ratio. Similarly, distance walked showed a progressive decrease along with HF severity. RERs registered in the last minute of the 6MWT were an average >1.0 in all HF groups, but they progressively increase as peak $\dot{V}O_2$ reduces. Of note, perceived fatigue as assessed by Borg symptoms scale was slightly but not significantly higher in HF subjects vs. healthy (3 [1–4.8] vs. 2 [1–3.25]), respectively.

Discussion

The main finding of our study is that the oxygen consumption reached during a standard 6MWT (6MWT-$\dot{V}O_2$) was similar to —or even higher than—that reached in CPET, particularly in more severe HF classes. This suggests that, from a metabolic point of view, a sizable portion of HF patients achieved, and maintained for at least 1 min, a maximal effort during brisk walking. Specifically, our results confirm how increasing numbers of patients exceed 110% of peak $\dot{V}O_2$ achieved at CPET as the severity of HF becomes greater (*Figure 2A* and *2B*).[6] It must be recognized that CPET and 6MWT are two different efforts. Indeed, a progressively workload test (CPET) is different from a constant workload test or from a test with self-adjusted workload, such as the 6MWT. Moreover, CPET was performed on a cycle ergometer, so that the muscle mass utilized is less than that used for walking and running, and consequently, our results should not be applied to CPET with a treadmill or other exercise tests as the shuttle test. In the present study, for $\dot{V}O_2$ comparison between biking and walking efforts, we considered a +10% correction factor, as previously reported,[21] being the oxygen uptake on the bike lower than the one observed during walking.[15,22,23]

The HF population we studied is characterized by relatively elderly male HF subjects. It represents a typical HF population seen in our HF ambulatory clinic. Of note, CPET and specifically peak VO_2 and VE/VCO_2 slope have been found to be very prognostic also in elderly HF patients.[24] A few previous reports addressed oxygen consumption in 6MWT.[4–6] Holland *et al*.[5] reported, in a study involving 47 patients with interstitial lung disease, that a significant proportion (45%) of subjects showed higher VO_2 values at 6MWT vs. maximal CPET, mostly in more severe disease. However, a comparison between cardiorespiratory parameters with the two tests in different HF settings is still undefined, particularly in patients with severe HF. It should be underlined, however, that it is unknown whether the presence of K5 influences *per se* the distance walked during the 6MWT, particularly in subjects with severe exercise limitation, albeit it is unlikely that major effects exist being K5 light (0.90 kg), easy wearable, and free of effects on subject's movement during a walk. In the present study, we wanted to compare metabolic data obtained with a maximal test on a cycle ergometer with those obtained during the execution of a 6MWT using a portable device in a sizable population of HF patients with different HF severity as well as in healthy subjects. Specifically, we analysed HR, $\dot{V}_E$, $\dot{V}O_2$, and SpO_2.

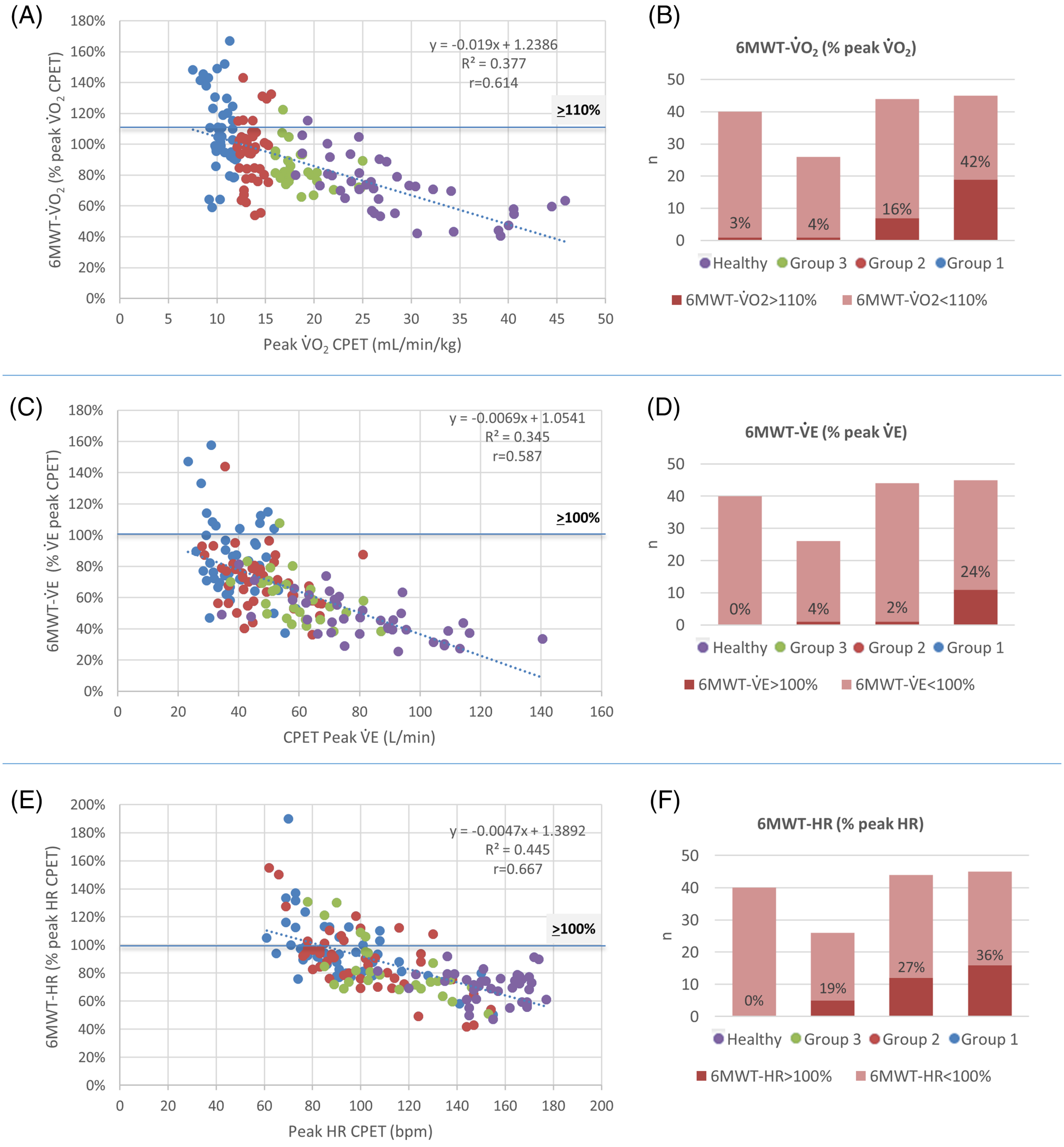
As for 6MWT, $\dot{V}_E$, and HR values, we detected in HF patients the tendency to exceed the values reached at CPET (*Figure 2C* and *2E*), a finding not present in healthy subjects. Interestingly, normal individuals never reached the maximum HR value achieved at CPET, while patients exceed their maximum value more frequently the more severe their disease are, being so in 36% of cases in the group with $\dot{V}O_2 < 12$ mL/kg/min (Group 1). Of note, the percentage of mildly impaired patients (Group 3) exceeding the maximum CPET HR value is higher than that for $\dot{V}O_2$ and $\dot{V}_E$ (*Figure 2B*, *2D*, and *2F*), suggesting a particularly important impact of 6MWT from the HR perspective. In parallel, the degree of activity above the ventilatory threshold, as assessable by RER recorded in the last minute of the 6MWT, was

Table 2 Metabolic data during cardiopulmonary exercise test and during 6 min walking test in the three groups of heart failure patients

	Group 1 $\dot{V}O_2 < 12$			Group 2 $\dot{V}O_2$ 12–16			Group 3 $\dot{V}O_2 > 16$					Bonferroni		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*P* for trend	ANOVA	g1 vs. g2	g2 vs. g3	g1 vs. g3
Cardiopulmonary exercise test														
Peak $\dot{V}O_2$ (mL/min)	45	776	160	44	1030	201	26	1367	230	<0.001	<0.001	<0.001	<0.001	<0.001
Peak $\dot{V}O_2$ (mL/kg/min)	45	10.44	1.11	44	13.54	0.96	26	18.80	2.68	<0.001	<0.001	<0.001	<0.001	<0.001
$\dot{V}_E/\dot{V}CO_2$ slope	44	40.9	10.4	44	38.1	8.7	26	31.6	5.3	<0.001	<0.001	0.410	0.010	<0.001
Peak $\dot{V}_E$ (L/min)	45	39.5	9.6	44	47.4	12.2	26	59.0	11.6	<0.001	<0.001	0.003	<0.001	<0.001
Peak RER	45	1.09	0.14	44	1.06	0.08	26	1.11	0.11	0.732	0.224			
$\dot{V}O_2$/work	30	7.64	1.71	44	8.33	1.62	24	9.59	0.86	<0.001	<0.001	0.190	0.005	<0.001
Rest HR (b.p.m.)	44	64	8	44	65	9	24	64	11	0.623	0.706			
Peak HR (b.p.m.)	45	92	21	44	100	23	26	111	21	0.005	0.002	0.255	0.121	0.002
Peak work (W)	45	60	19	44	79	18	26	105	22	<0.001	0.00	<0.001	<0.001	<0.001
6 min walking test														
Rest $\dot{V}O_2$ 6MWT (L/min)	45	519	128	44	513	139	26	482	161	0.320	0.545			
$\dot{V}O_2$ 6MWT (L/min)	45	835	225	44	975	267	26	1147	237	<0.001	<0.001	0.024	0.016	<0.001
$\dot{V}O_2$ 6MWT (mL/kg/min)	45	11.3	2.5	44	12.7	3.1	26	15.6	2.4	<0.001	<0.001	0.043	<0.001	<0.001
$\dot{V}O_2$ 6MWT (% peak $\dot{V}O_2$)	45	109%	0.3	43	94%	0.2	26	84%	0.1	<0.001	<0.001	0.004	0.213	<0.001
$\dot{V}_E$ 6MWT (L)	45	32.5	9.9	44	33.0	9.8	26	34.3	7.9	0.439	0.728			
VT 6MWT	44	1.1	0.3	44	1.2	0.3	26	1.2	0.3	0.321	0.357			
$\dot{V}_E/\dot{V}CO_2$ 6MWT	45	49.6	6.8	44	43.9	6.9	26	38.8	5.9	<0.001	<0.001	<0.001	0.007	<0.001
Rest HR 6MWH (b.p.m.)	44	71	10	44	70	11	26	69	12	0.598	0.864			
HR 6MWT (b.p.m.)	45	86	16	44	87	18	26	90	15	0.415	0.645			
$PetO_2$ 6MWT (mmHg)	45	113.2	5.7	44	110.9	5.2	26	108.1	3.8	<0.001	0.001	0.109	0.095	<0.001
$PetCO_2$ 6MWT(mmHg)	45	28.3	3.4	44	30.7	4.1	26	34.4	3.7	<0.001	<0.001	0.008	<0.001	<0.001
$\dot{V}CO_2$ 6MWT (mL/min)	45	655	181	44	767	204	26	897	199	<0.001	<0.001	0.023	0.025	<0.001
RER 6MWT	45	1.11	0.14	44	1.05	0.16	26	1.02	0.09	0.004	0.013	0.089	1.000	0.020
Distance 6MWT (m)	44	340	88	44	405	72	26	449	76	<0.001	<0.001	0.001	0.079	<0.001
SpO_2 basal 6MWT (%)	43	97	2	44	97	2	26	97	1	0.227	0.442			
SpO_2 stop 6MWT (%)	43	95	3	44	96	2	26	97	2	0.007	0.024	0.150	1.00	0.030
Borg scale	45	3 [1–5]		44	2 [1–4]		26	3 [1–4]		0.517	0.507			

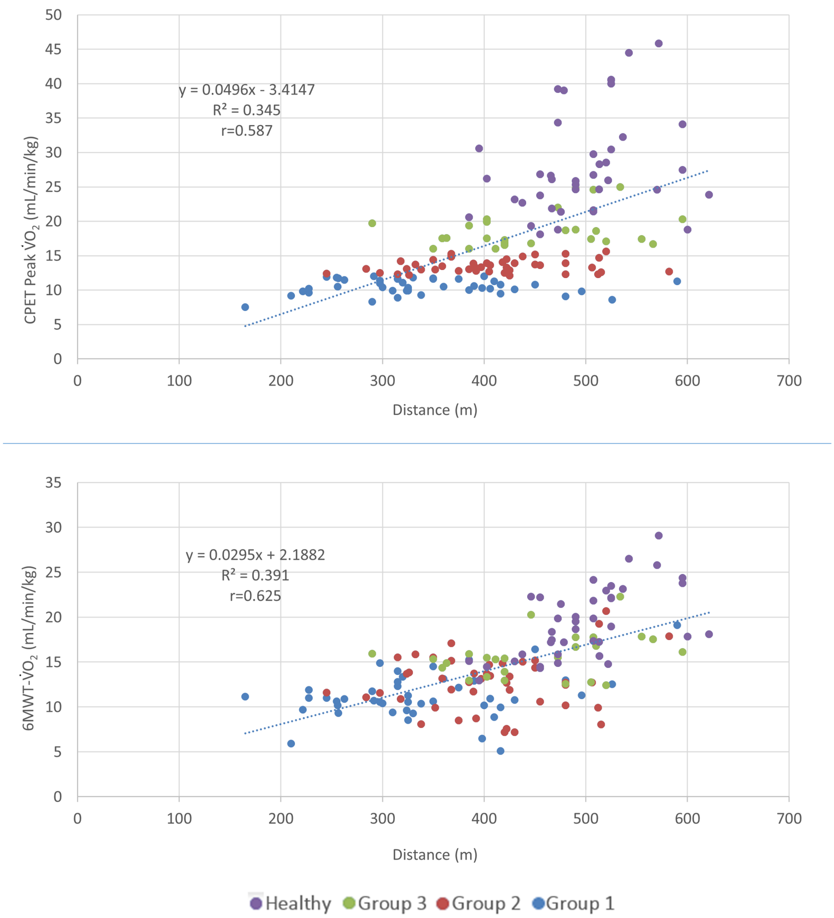
6MWT, 6 min walking test; HR, heart rate; Peak, peak exercise at cardiopulmonary exercise test; $PetCO_2$, end-tidal carbon dioxide pressure; $PetO_2$, end-tidal oxygen pressure; RER, respiratory gas exchange; SpO_2, haemoglobin oxygen saturation; $\dot{V}CO_2$, expired CO_2 volume; $\dot{V}_E$, ventilation; $\dot{V}O_2$, oxygen uptake; VT, tidal volume.

Figure 2 (A) The correlation between oxygen uptake (peak$\dot{V}O_2$) at cardiopulmonary exercise test (CPET) and 6 min walking test-$\dot{V}O_2$ expressed as a per cent of the CPET peak $\dot{V}O_2$ (6MWT-$\dot{V}O_2$%) is shown. In (B), we show the percentage of subjects overcoming the 110% of CPET peak $\dot{V}O_2$ for each subgroup (healthy, Group 1 = peak $\dot{V}O_2 < 12$ mL/kg/min, Group 2 = peak $\dot{V}O_2$ 12–16 mL/kg/min, and Group 3 = peak $\dot{V}O_2 > 16$ mL/kg/min). (C) The correlation between peak ventilation ($\dot{V}_E$) and 6MWT-$\dot{V}_E$ expressed as % of peak $\dot{V}_E$ at CPET (6MWT-$\dot{V}_E$ %) is shown. In (D), the percentage of subjects overcoming the 100% of CPET peak $\dot{V}_E$ for each subgroup is reported. (E) The correlation between peak heart rate (HR) and 6MWT-HR as % of peak HR at CPET (6MWT-HR%). In (F), the percentage of subjects overcoming the 100% of CPET peak HR for each subgroup.



lower in healthy subjects compared with HF cases and, among HF patients, the highest in patients with more severe exercise limitation. Borg scale values, as well as O_2 and CO_2 end-tidal pressures values (*Tables 1* and *2*), are confirmative of RER values. Altogether, these findings suggest that, at least for the last minute, the 6MWT in severe HF patients is a maximal or even supramaximal effort compared with standard cycle-ergometer CPET so that 6MWT should not be considered as a less demanding challenge with respect to CPET in HF subjects. Indeed, inside each category of subjects, grouped according to exercise performance, the greater the 6MWT-$\dot{V}O_2$, the greater is the use of aerobic metabolism if reported as a percentage of peak $\dot{V}O_2$ at CPET (6MWT-$\dot{V}O_2$%). Therefore, in patients with severe HF, even

Figure 3 Upper panel: correlation between the distance covered during a 6 min walking test (6MWT) and oxygen uptake (peak$\dot{V}O_2$) at the cardiopulmonary exercise test (CPET). Lower panel: correlation between the distance covered during 6MWT and 6MWT-$\dot{V}O_2$.

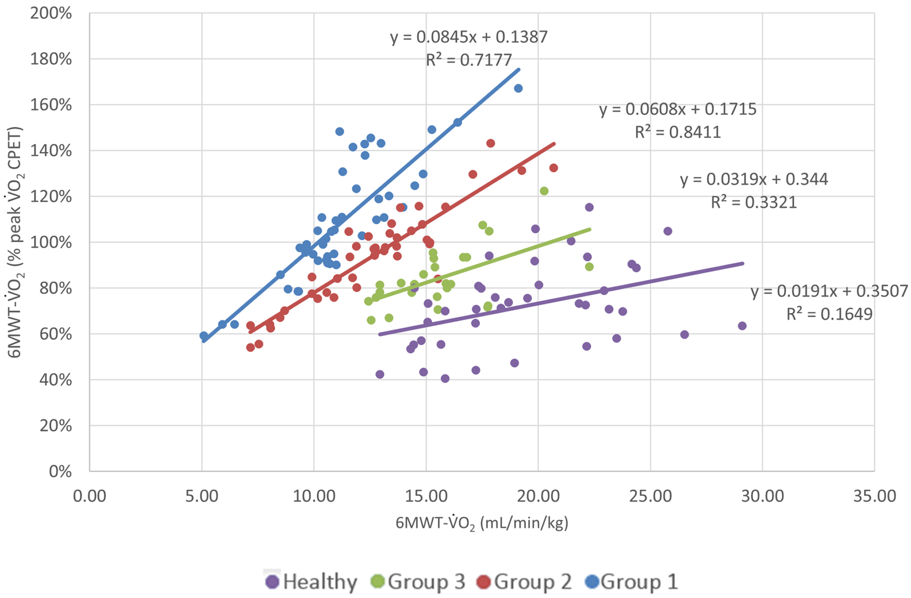


a small increase in 6MWT-$\dot{V}O_2$ leads to an exhaustion of the aerobic metabolism possible in these cases, as shown by the steepness of the 6MWT-$\dot{V}O_2$% vs. 6MWT-$\dot{V}O_2$ relationship (*Figure 4*).

The CPET and 6MWT are two widely used tools for the functional classification of patients with HF. Between the two, there is often a tendency to lean towards the latter, both because of its simplicity of execution (it requires less equipment and simpler training for staff) and because it is generally considered as a test with lower risks for more severe patients. Major adverse events associated with exercise during clinical investigations, both CPET and 6MWT, are in fact very rare.[25] Of note, post-exercise acute pulmonary oedema is a possible consequence of maximal exercise[26] in HF, albeit usually neglected as a direct consequence of it, as it appears sometime after the effort. SpO_2 results showed a significant tendency towards lower values in severe HF patients, albeit always in the range of what is defined clinically normal. This finding is physiologically interesting. Indeed, reduction of SpO_2 has been demonstrated at peak exercise in healthy subjects, but only in elite athletes.[27] This has been explained by the presence at peak exercise of some venous admixture flow and/or by an increase speed of capillary transit combined with lower mixed venous SpO_2, which may not allow complete haemoglobin saturation at the level of some low efficiency alveolar/capillary units.[28] Moreover, it is believed that in HF, a reduction of SpO_2 implies the presence of concomitant lung disease.[29] The present study finding of a significant (although minor and not clinically relevant) SpO_2 reduction at peak exercise in severe HF patients performing 6MWT confirms that it can be a maximal or even a supramaximal exercise and shows why alveolar capillary gas diffusion abnormalities are strongly associated with exercise performance in HF.[30] Indeed, Hb O_2 desaturation implies a derangement between the three factors at play at the alveolar capillary membrane level: alveolar capillary diffusion capacity, oxygen flow, and alveolar capillary oxygen pressure gradient.[31] Accordingly, to maintain SpO_2, the alveolar capillary pO_2 gradient must increase, which means further ventilation and work of breathing.

DOI: 10.1002/ehf2.13781

Figure 4 Correlation between the 6 min walking test-$\dot{V}O_2$ expressed as an absolute value (6MWT-$\dot{V}O_2$) and as a per cent of the CPET peak $\dot{V}O_2$ (6MWT-$\dot{V}O_2$%). The slope of the 6MWT-$\dot{V}O_2$% vs. 6MWT-$\dot{V}O_2$ relationship progressively increased as exercise limitation did.



A few study limitations must be recognized. First, wearable K5 and stationary Quark differ for the CO_2 transducer. Second, in the present study, we compared 6MWT and CPET on a cycle ergometer. Therefore, our data cannot be extended to other ergometers such as treadmills or to other walking tests such as the shuttle test. Third, the order between 6MWT and CPET was not randomized. Indeed, because CPETs were performed first, we cannot completely exclude a training effect of CPET on 6MWT albeit all patients had previous experience with both tests.

In conclusion, at least the last minute of 6MWT must be perceived as a maximal or even supramaximal exercise activity. Albeit it is reported as a safe procedure, it is not clear why safety precautions should be different from those needed in a standard CPET.

Acknowledgements

We thank Mrs Michela Palmieri and Mrs Edda Podella for the English revision of the text.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Funding

None.

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