


# Taking a walk on the heart failure side: comparison of metabolic variables during walking and maximal exertion

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## Abstract

**Aims** Although cardiopulmonary exercise testing (CPET) is the gold standard to assess exercise capacity, simpler tests (i.e., 6-min walk test, 6MWT) are also commonly used. The aim of this study was to evaluate the relationship between cardiorespiratory parameters during CPET and 6MWT in a large, multicentre, heterogeneous population.

**Methods** We included athletes, healthy subjects, and heart failure (HF) patients of different severity, including left ventricular assist device (LVAD) carriers, who underwent both CPET and 6MWT with oxygen consumption measurement.

**Results** We enrolled 186 subjects (16 athletes, 40 healthy, 115 non-LVAD HF patients, and 15 LVAD carriers). CPET-peak $\dot{V}O_2$  was 41.0 [35.0–45.8], 26.2 [23.1–31.0], 12.8 [11.1–15.3], and 15.2 [13.6–15.6] ml/Kg/min in athletes, healthy, HF patients, and LVAD carriers, respectively ( $P < 0.001$ ). During 6MWT they used 63.5 [56.3–76.8], 72.0 [57.8–81.0], 95.5 [80.3–109], and 95.0 [92.0–99.0] % of their peak $\dot{V}O_2$ , respectively. None of the athletes, 1 healthy (2.5%), 30 HF patients (26.1%), and 1 LVAD carrier (6.7%), reached a 6MWT- $\dot{V}O_2$  higher than their CPET-peak $\dot{V}O_2$ . Both 6MWT- $\dot{V}O_2$  and walked distance were significantly associated with CPET-peak $\dot{V}O_2$  in the whole population ( $R^2 = 0.637$  and  $R^2 = 0.533$ ,  $P \leq 0.001$ ) but not in the sub-groups. This was confirmed after adjustment for groups.

**Conclusions** The 6MWT can be a maximal effort especially in most severe HF patients and suggest that, in absence of prognostic studies related to 6MWT metabolic values, CPET should remain the first method of choice in the functional assessment of patients with HF as well as in sport medicine.

**Keywords** 6-min walk test; Cardiopulmonary exercise test; CPET; Heart failure; K5

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## Background

Maximal cardiopulmonary exercise testing (CPET) is the most accurate method to measure exercise performance in different populations, including healthy subjects, athletes, and patients with heart failure (HF).<sup>1,2</sup> In this latter condition, peak exercise oxygen uptake (peak $\dot{V}O_2$ ) provides relevant prognostic information.<sup>3</sup> However, due to the limited availability of

CPET, exercise performance is usually assessed by simpler tests such as the 6-min walk test (6MWT). As a matter of facts, peak $\dot{V}O_2$  and 6MWT distance are considered interchangeable as regards HF performance evaluation and prognosis. However, this is not the case being 6MWT affected not only by CPET determinants such as respiratory, circulatory, and metabolic functions, but also by lower limb muscle strength and balance ability.<sup>4,5</sup> In any case, the 6MWT is gen-

erally considered a submaximal (and therefore safer) test, recent trials<sup>6–8</sup> demonstrated how daily-life activities, including a brisk walk, represent maximal exercises from a metabolic point of view for many HF patients.<sup>9</sup> This is particularly evident for the most severe patients, in which the  $\dot{V}O_2$  measured during 6MWT exceed the peak $\dot{V}O_2$  in almost half of the cases.<sup>6</sup> To date, few studies limited to HF patients with inconclusive results<sup>10,11</sup> address the relationship between the oxygen uptake during a 6MWT and a maximal exercise in different subjects are still lacking.

## Aims

The aim of this study was to assess the relationship between the cardiorespiratory parameters collected during maximal CPET and 6MWT in a large, multicentre, heterogeneous group of subjects including athletes, healthy subjects, patients with HF of different severity including left ventricular assist device (LVAD) carriers.

## Methods

HF patients (including LVAD carriers), healthy subjects, and athletes were recruited at Heart Failure Units of Centro Cardiologico Monzino IRCCS, Istituti Clinici Scientifici Maugeri IRCCS, and Department of Cardiology, University of Copenha-

gen, Rigshospitalet. None of the healthy subjects or athletes was on treatment with any drugs possibly affecting the cardiorespiratory system. In all study locations, subjects underwent the same exercise protocol and data analysis, for both CPET and 6MWT. HF 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. All HF patients were evaluated by echocardiography to determine left ventricular ejection fraction (LVEF, Simpson biplane method).<sup>6</sup> 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.<sup>12,13</sup> Exclusion criteria were the use of long-term oxygen therapy, previous heart transplantation, neuromuscular co-morbidities affecting the possibility to perform exercise tests, and concomitant moderate or severe chronic obstructive pulmonary disease.<sup>14</sup> CPETs were performed by means of a stationary ergospirometer (Quark PFT, COSMED, Rome, Italy) using an electronically braked cycle ergometer and peak $\dot{V}O_2$  was measured as previously described.<sup>3,15,16</sup> According to their CPET  $\dot{V}O_2$ , non-LVAD HF patients were divided in three groups (Group1, <12; Group2, 12–16; and Group3, >16 mL/kg/min. 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), as previously described.<sup>6,17–19</sup>

**Table 1** Study variables in healthy in HF subjects

	Healthy (N = 56)	HF (N = 130)	All (N = 186)	P
Height (m)	174 [168, 179]	172 [166, 178]	173 [167, 178]	0.304
Weight (kg)	75.1 [69.8, 85.3]	75.0 [68.0, 86.8]	75.0 [69.0, 86.0]	0.87
BMI (kg/m <sup>2</sup> )	24.8 [23.4, 27.8]	25.5 [23.9, 28.1]	25.3 [23.7, 28.1]	0.31
Age (years)	60.5 [55.8, 64.0]	70.0 [64.0, 75.0]	67.0 [59.3, 73.0]	<0.001
Females	13 (23.2%)	23 (17.7%)	36 (19.4%)	0.502
Males	43 (76.8%)	107 (82.3%)	150 (80.6%)	
Haemoglobin (g/dL)	14.8 [14.5, 15.02]	13.3 [12.3, 14.2]	13.5 [12.4, 14.3]	<0.001
LVEF (%)	NA	26.4 [32–39.4]	NA	-
PAPs (mmHg)	NA	29 [35–45]	NA	-
<b>CPET data</b>				
CPET-peak $\dot{V}O_2$ (mL/min)	2,300 [1820, 3,090]	1,010 [820, 1,250]	1,200 [888, 1720]	<0.001
CPET-peak $\dot{V}O_2$ (mL/min/kg)	28.4 [24.6, 39.4]	13.1 [11.3, 15.4]	15.2 [12.0, 23.8]	<0.001
CPET-peak $\dot{V}O_2$ (% of pred)	112 [92.5, 137]	56.2 [49.0, 66.0]	64.0 [52.0, 92.5]	<0.001
VE/ $\dot{V}CO_2$ slope	28.8 [26.2, 31.4]	36.0 [31.4, 43.6]	33.9 [28.5, 40.7]	<0.001
Peak heart rate (b.p.m.)	154 [145, 166]	98.0 [85.0, 123]	116 [90.0, 148]	<0.001
Peak workload (Watt)	189 [150, 224]	75.0 [60.0, 99.0]	93.5 [67.0, 133]	<0.001
<b>6MWT data</b>				
Rest heart rate (b.p.m.)	78.0 [69.0, 90.0]	70.0 [61.0, 80.0]	72.0 [65.0, 82.0]	<0.001
End heart rate (b.p.m.)	112 [100, 125]	86.0 [76.0, 100]	96.0 [79.5, 111]	<0.001
6MWT- $\dot{V}O_2$ (mL/min)	1,550 [1,250, 1920]	971 [792, 1,190]	1,090 [844, 1,380]	<0.001
6MWT- $\dot{V}O_2$ (mL/min/kg)	21.8 [17.2, 23.9]	12.9 [10.8, 15.1]	14.5 [11.7, 17.8]	<0.001
Task $\dot{V}O_2$ (%of peak)	0.710 [0.578, 0.810]	0.950 [0.820, 1.08]	0.900 [0.730, 1.03]	<0.001
6MWT VE/ $\dot{V}CO_2$	30.8 [29.5, 32.7]	43.2 [39.2, 49.4]	39.7 [32.3, 46.7]	<0.001
Distance (m)	524 [473, 631]	397 [326, 450]	430 [362, 509]	<0.001

6MWT, 6-min walking test; 6MWT- $\dot{V}O_2$ , oxygen uptake at 6MWT; BMI, body mass index; CPET, cardiopulmonary exercise test; CPET-peak $\dot{V}O_2$ , oxygen uptake at peak exercise at CPET; Task  $\dot{V}O_2$ , oxygen uptake expressed as percentage of the oxygen uptake at peak exercise at CPET; VE/ $\dot{V}CO_2$ , ventilation versus  $\dot{V}CO_2$  production; HF, heart failure.

Table 2 Study variables according to the subgroups

	Athletes (N = 16)	Healthy (N = 40)	HF (no LVAD) (N = 115)	LVAD (N = 15)	All (N = 186)	P
Height (m)	179 [175, 182]	171 [164, 178]	170 [165, 176]	183 [179, 189]	173 [167, 178]	<0.001
Weight (kg)	87.8 [76.2, 94.8]	73.0 [68.0, 80.0]	74.0 [67.0, 83.0]	93.0 [81.5, 105]	75.0 [69.0, 86.0]	<0.001
BMI (kg/m <sup>2</sup> )	26.7 [24.1, 27.7]	24.7 [23.2, 27.4]	25.3 [23.7, 28.0]	27.7 [25.0, 30.4]	25.3 [23.7, 28.1]	0.0632
Age (years)	60.5 [59.0, 64.5]	60.5 [54.8, 63.3]	71.0 [65.0, 76.0]	65.0 [56.5, 68.0]	67.0 [59.3, 73.0]	<0.001
Females	0 (0%)	13 (32.5%)	23 (20.0%)	0 (0%)	36 (19.4%)	
Males	16 (100%)	27 (67.5%)	92 (80.0%)	15 (100%)	150 (80.6%)	0.00774
Haemoglobin (g/dL)	14.8 [14.5, 15.02]	NA	13.3 [12.3, 14.2]	13.8 [12.3, 14.6]	12.6 [10.7, 14.0]	<0.001
LVEF (%)	NA	NA	26.4 [32–39.4]	NA	-	-
PAPs (mmHg)	NA	NA	29 [35–45]	NA	-	-
<b>CPET data</b>						
CPET-peak $\dot{V}O_2$ (mL/min)	3,440 [3,050, 3,690]	1910 [1,660, 2,370]	966 [793, 1,190]	1,450 [1,220, 1,530]	1,200 [888, 1720]	<0.001
CPET-peak $\dot{V}O_2$ (mL/min/kg)	41.0 [35.0, 45.8]	26.2 [23.1, 31.0]	12.8 [11.1, 15.3]	15.2 [13.6, 15.6]	15.2 [12.0, 23.8]	<0.001
CPET-peak $\dot{V}O_2$ (% of pred)	145 [127, 163]	102 [91.0, 122]	57.0 [49.5, 67.0]	55.8 [46.3, 57.4]	64.0 [52.0, 92.5]	<0.001
VE/VCO <sub>2</sub> slope	31.8 [30.0, 34.3]	26.9 [24.3, 30.0]	35.8 [31.0, 43.9]	37.9 [34.6, 42.7]	33.9 [28.5, 40.7]	<0.001
Peak heart rate (b.p.m.)	152 [146, 157]	155 [145, 167]	95.0 [83.5, 114]	131 [119, 151]	116 [90.0, 148]	<0.001
Peak workload (Watt)	225 [175, 275]	175 [132, 201]	72.0 [57.5, 99.0]	75.0 [75.0, 99.0]	93.5 [67.0, 133]	<0.001
Rest heart rate (b.p.m.)	75.0 [67.0, 91.0]	80.0 [69.8, 90.0]	70.0 [61.0, 78.8]	80.0 [76.3, 80.0]	72.0 [65.0, 82.0]	<0.001
End heart rate (b.p.m.)	125 [121, 130]	107 [97.0, 121]	84.0 [75.0, 97.5]	126 [103, 138]	96.0 [79.5, 111]	<0.001
6MWT- $\dot{V}O_2$ (mL/min)	2,180 [1930, 2,580]	1,370 [1,190, 1,610]	937 [772, 1,100]	1,320 [1,130, 1,400]	1,090 [844, 1,380]	<0.001
6MWT- $\dot{V}O_2$ (mL/min/kg)	24.8 [22.5, 27.5]	18.8 [15.8, 22.2]	12.7 [10.6, 15.0]	14.4 [13.0, 15.1]	14.5 [11.7, 17.8]	<0.001
Task $\dot{V}O_2$ (% of peak)	0.635 [0.563, 0.768]	0.720 [0.578, 0.810]	0.955 [0.803, 1.09]	0.950 [0.920, 0.990]	0.900 [0.730, 1.03]	<0.001
6MWT VE/VCO <sub>2</sub>	29.3 [27.7, 29.8]	31.6 [30.3, 33.7]	44.2 [39.8, 49.9]	38.7 [35.5, 40.6]	39.7 [32.3, 46.7]	<0.001
Distance (m)	765 [686, 825]	499 [466, 525]	391 [325, 449]	420 [390, 470]	430 [362, 509]	<0.001

6MWT, 6-min walking test; 6MWT- $\dot{V}O_2$ , oxygen uptake at 6MWT; BMI, body mass index; CPET, cardiopulmonary exercise test; CPET-peak $\dot{V}O_2$ , oxygen uptake at peak exercise at CPET; HF, heart failure; Task  $\dot{V}O_2$ , oxygen uptake expressed as percentage of the oxygen uptake at peak exercise at CPET; VE/VCO<sub>2</sub>, ventilation versus CO<sub>2</sub> production.

## Statistical analysis

Continuous variables are reported as median and interquartile range as appropriate for non-normally distributed parameters. Categorical variables are presented as n and percentage. Between groups comparison was done by Mann–Whitney *U* test or Kruskal–Wallis as appropriate, while chi-squared test was used for categorical variables.

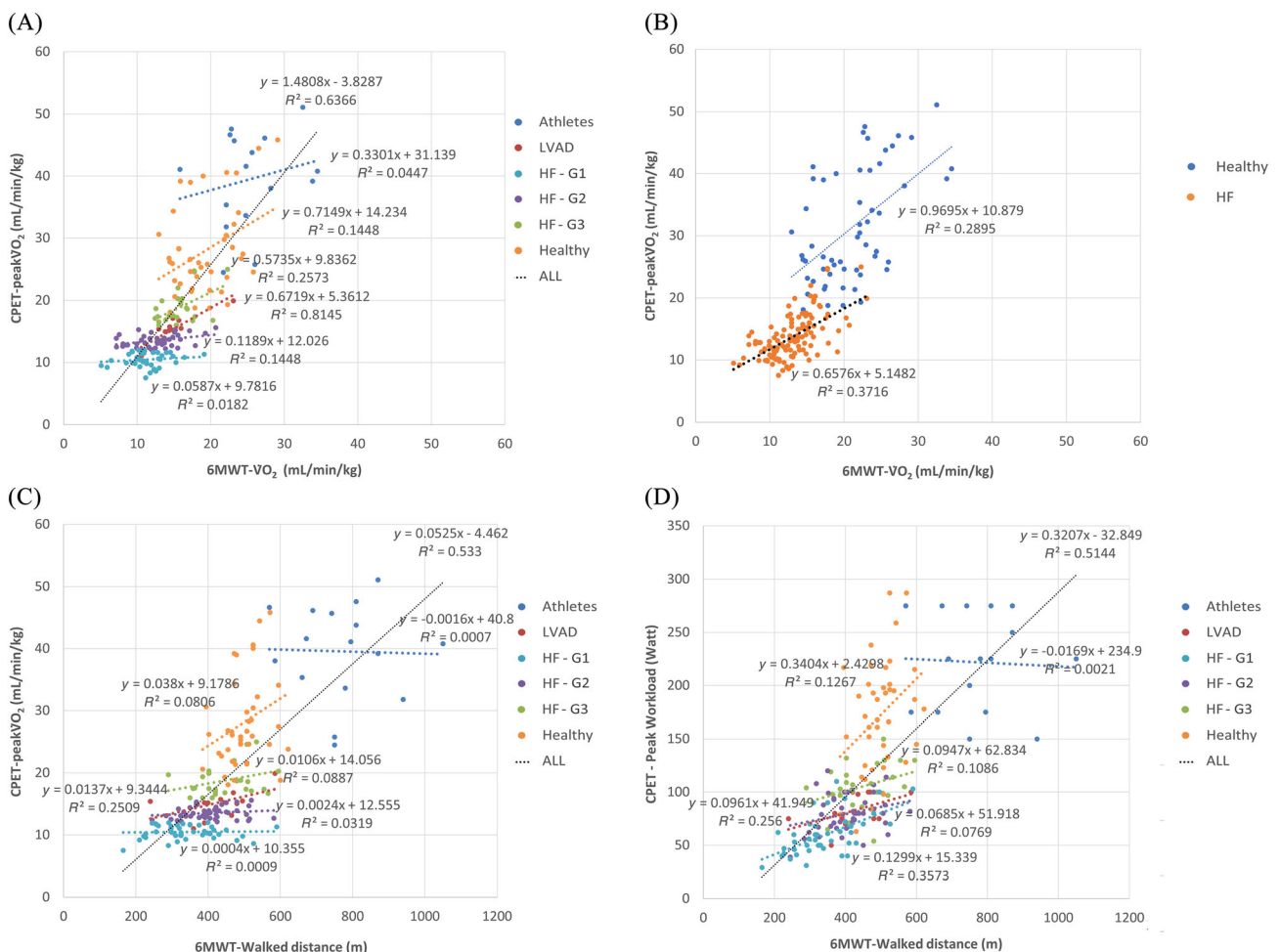
Association of variables are shown as linear regressions.  $R^2$  were also calculated by multivariable linear regressions with group variable (athletes, healthy subjects, HF patients and LVAD patients) as covariate.

A *P*-value <0.05 was used to define statistical significance. All statistical analyses were performed using IBM SPSS Statistics v. 27.

## Results

One hundred and eighty-six subjects were enrolled (16 athletes, 40 healthy, 115 non-LVAD HF patients, and 15 LVAD carriers) and completed the study procedures with no significant adverse events. *Table 1* shows the main characteristics of the population and their metabolic values with significance between healthy subjects and HF patients. According to exercise limitation severity, HF patients showed higher  $\dot{V}E/\dot{V}CO_2$  slope (*Table 1*). In *Table 2*, results are presented according to the four study groups (athletes, healthy, HF patients, and LVAD carriers). CPET-peak $\dot{V}O_2$  was 41.0 [35.0, 45.8], 26.2 [23.1, 31.0], 12.8 [11.1, 15.3], and 15.2 [13.6, 15.6] ml/Kg/min (corresponding to 145 [127, 163], 102 [91.0, 122], 57.0 [49.5, 67.0], and 57.0 [49.5, 67.0]% of the predicted) in ath-

**Figure 1** Correlations between CPET variables and 6MWT. In the upper part of the figure we show the linear regressions between CPET-peak $\dot{V}O_2$  and 6MWT- $\dot{V}O_2$  in the whole population and in the subgroups (panel A), and according to the presence of HF (panel B). In the lower part of the figure, walked distance at 6MWT is correlated with CPET- $\dot{V}O_2$  (panel C) and with CPET peak workload (panel D). 6MWT, 6-min walking test; 6MWT- $\dot{V}O_2$  = oxygen uptake at 6MWT; CPET, cardiopulmonary exercise test; CPET-peak $\dot{V}O_2$ , oxygen uptake at peak exercise; HF, heart failure.



letes, healthy, HF patients, and LVAD carriers, respectively ( $P < 0.001$ ). During 6MWT athletes, healthy, HF patients, and LVAD carriers used 63.5 [56.3, 76.8], 72.0 [57.8, 81.0], 95.5 [80.3, 109], and 95.0 [92.0, 99.0] % of their peak $\dot{V}O_2$ , respectively. The correlations between CPET-peak $\dot{V}O_2$  and 6MWT- $\dot{V}O_2$  are shown in *Figure 1*. Panel A shows relationship between the two values in the whole population ( $R^2 = 0.6366$ ,  $P \leq 0.001$ ) and in the different groups of subjects, including HF patient subgroups divided according to the CPET-peak $\dot{V}O_2$ . Panel B shows the correlation in non-HF patients (healthy and athletes combined) in comparison with HF patients (both LVAD and non-LVAD carriers) ( $R^2 = 0.2895$  and  $0.3716$ , respectively). None of the athletes, 1 healthy (2.5%), 30 HF patients (26.1%), and 1 LVAD carrier (6.7%), reached a  $\dot{V}O_2$  during 6MWT higher than 110% of their measured peak  $\dot{V}O_2$ . The value of 110% of peak  $\dot{V}O_2$  at CPET was chosen to consider the differences in the metabolism cost of walking (6MWT) versus cycling (CPET). Further, at multivariate analysis the association between the  $\dot{V}O_2$  at CPET and at 6MWT was still significant after adjustment for groups, but with lower  $R^2$  within each group analysed except for LVAD patients ( $R^2 = 0.335$  for HF patients,  $0.798$  for LVAD,  $-0.024$  for athletes,  $0.122$  for healthy subjects,  $0.633$  for the entire population).

We also analysed in all the study groups the regressions between walked distance at 6MWT and peak $\dot{V}O_2$  (panel C) or workload (panel D) at CPET.

## Conclusion

Our study demonstrated for the first time in a broad population, that  $\dot{V}O_2$  values obtained during a standard 6MWT are significantly related to the peak $\dot{V}O_2$  measured with a maximal CPET, generally considered the gold standard method to assess functional capacity. On average 6MWT- $\dot{V}O_2$  can elicit  $75.3 \pm 33.8\%$  of the CPET  $\dot{V}O_2$ , but this ratio can be extremely variable depending on the population considered. In fact, as previously described in three recent trials,<sup>6–8</sup> the more severe the patient with HF, the more they consume their ' $\dot{V}O_2$  reserve', going so far as to erode it in 42% of cases in patients with CPET  $\dot{V}O_2$  below 12 mL/kg/min. Interestingly, LVAD carriers showed metabolic behaviour similar to the one of their non-LVAD HF patients counterpart since, with an exercise capacity similar to the one of severe HF patients (peak $\dot{V}O_2$  14.9 mL/kg/min, 53.8% of the predicted, and  $\dot{V}E/\dot{V}CO_2$  slope 38.6) their 6MWT- $\dot{V}O_2$  corresponds to 95.9% of CPET  $\dot{V}O_2$ , a value similar to the one of 'moderate' HF subjects (see *Table 1*, Group 2). Of note, both LVAD and HF group 1 patients have a flat correlation between peak $\dot{V}O_2$  at CPET and  $\dot{V}O_2$  at 6MWT, suggesting that walking is much better tolerated than cycling in these patients possibly due the overall greater muscle mass utilized with walking. On the other hand, in highly

trained subjects (athletes group showed an average peak $\dot{V}O_2$  of 39.6 mL/kg/min), the 6MWT- $\dot{V}O_2$  corresponded to 66.7% of their CPET  $\dot{V}O_2$ , demonstrating how far from a maximal exercise they are while walking. The different  $\dot{V}O_2$  behaviour in HF and healthy during maximal CPET and 6MWT deserves some comments. Despite a general good correlation of the two parameters in the whole cohort ( $R^2 = 0.6366$ ), dividing the population in non-HF and HF subjects (*Figure 1B*) results in a significant reduction in the goodness of correlation ( $R^2 < 0.4$  for both), even if a significant group effect at the multivariate analysis was not present. In other words, the ability to predict peak $\dot{V}O_2$  based on the  $\dot{V}O_2$  values obtained at 6MWT appears to be rather limited, particularly in patients with HF. Also in the athletes' subgroup, the correlation between 6MWT- $\dot{V}O_2$  and CPET  $\dot{V}O_2$  is low, probably due to an even wider delta between the  $\dot{V}O_2$  elicited in the two different exercises related to the extreme fitness of some muscle groups and to the intrinsic characteristics of 6MWT: a fixed execution time, the frequent and sudden direction change and the physical constrains related to type of exercise (a walk), making hard for a well-trained individual to reach a truly maximal effort.

Similar considerations come from the analysis of the regressions between walked distance at 6MWT and peak $\dot{V}O_2$  (panel C) or workload (panel D) at CPET, suggesting that estimating the exercise capacity from 6MWT can lead to a non-negligible error. In fact, considering subjects of the same type (HF patients, athletes, etc.) the variability is very high. Finally, our study compared metabolic values obtained during different types of exercise: walking during 6MWT and cycling during CPET. Indeed, few are the reasons for a difference in the metabolic cost of walking/running versus cycling including the walking/running greater muscle mass at work and the metabolic cost of up-lifting the abdomen which is relevant in case of overweight subjects. We considered these differences by using 110% of predicted  $\dot{V}O_2$  cycling value as suggested by Wasserman.<sup>16,20–22</sup> However, we opted for cycloergometer instead of treadmill mainly for safety reason, being the cycloergometer generally better tolerated especially in frail subjects like severe HF patients and LVAD carriers.

In conclusion, these data confirm that 6MWT can be a maximal effort especially in most severe HF patients and suggest that, in absence of prognostic studies related to 6MWT metabolic values, CPET should remain the first method of choice in the functional assessment of patients with HF as well as in sport medicine.

## Conflict of interest

The authors certify that they have no conflict of interest.

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