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 (peakVO2). 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 peakVO2 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-VO2 was 98 ± 20% of the CPET peakVO2 values in HF patients, while 72 ± 20% in healthy subjects (P < 0.001). 6MWT-VO2 was >110% of CPET peakVO2 in 42% of more severe HF patients (peakVO2 < 12 mL/kg/min). Similar results have been found for ventilation and heart rate. Of note, the slope of the relationship between VO2 at 6MWT, reported as a percentage of CPET peakVO2 vs. 6MWT VO2 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

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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 VO2). 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 VO2 and the distance walked at 6MWT.3–7 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 (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 ultrasound13 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.9 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 (V6). V6 vs. carbon dioxide production (V6/VO2) slope was calculated as the slope of the linear relationship between V6 and VCO2 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 VCO2/VO2, 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 VO2, V6, and VCO2 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 (SpO₂) 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 (V̇O₂ and V̇E).

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 V̇O₂: <12, 12–16, and >16 mL/kg/min.

Oxygen uptake during 6MWT (6MWT-V̇O₂) was calculated and expressed both as mL/kg/min and as a per cent of the peak V̇O₂ 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 V̇O₂ were 1.90% of the recorded breaths. A similar percentage of breaths were removed for the other analysed variables.
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/m²) and 115 were HF patients (69 ± 10 years; male 80%, body mass index 26.2 ± 4.3 kg/m²; 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 VO₂: 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 walk test in healthy subjects and heart failure patients |
|---------|---------------------------------------------------------------|
|         | Healthy subjects (n = 40) | Patients (n = 115) | P      |
|         | n  | Mean | SD  | n  | Mean | SD  |      |
| **Cardiopulmonary exercise test** | | | | | | | |
| Peak VO₂ (ml/min) | 40 | 2047 | 581 | 115 | 1008 | 296 | <0.001 |
| Peak VO₂ (ml/kg/min) | 40 | 28.1 | 7.4 | 115 | 13.5 | 3.5 | <0.001 |
| V̇E/CO₂ 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 |
| VO₂/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 VO₂ 6MWT (L/min) | 40 | 428 | 97 | 115 | 508 | 140 | 0.001 |
| VO₂ 6MWT (L/min) | 40 | 1410 | 317 | 115 | 959 | 270 | <0.001 |
| VO₂ 6MWT (ml/kg/min) | 40 | 19.4 | 3.9 | 115 | 12.8 | 3.2 | <0.001 |
| VO₂ 6MWT (% peak VO₂) | 40 | 72% | 20% | 114 | 98% | 20% | <0.001 |
| V̇E 6MWT (L/min) | 40 | 36.1 | 8.8 | 114 | 33.1 | 9.4 | 0.079 |
| VT 6MWT (L) | 40 | 1.5 | 0.4 | 114 | 1.2 | 0.3 | <0.001 |
| V̇E/CO₂ 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 |
| PetO₂ 6MWT (mmHg) | 40 | 104.9 | 3.6 | 115 | 111.1 | 5.4 | <0.001 |
| PetCO₂ 6MWT (mmHg) | 40 | 39.0 | 3.0 | 114 | 30.6 | 4.4 | <0.001 |
| V̇CO₂ 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 |
| SpO₂ basal 6MWT (%) | 40 | 97.9 | 0.9 | 113 | 97.1 | 1.5 | 0.001 |
| SpO₂ 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; PetCO₂, end-tidal carbon dioxide pressure; PetO₂, end-tidal oxygen pressure; RER, respiratory gas exchange; SpO₂, haemoglobin oxygen saturation; V̇CO₂, expired CO₂ volume; V̇E, ventilation; VO₂, 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 V\textsubscript{E}/VO\textsubscript{2} slope and lower peak workload and VO\textsubscript{2}/work values (Table 2).

The correlation between peak VO\textsubscript{2} at CPET and 6MWT-VO\textsubscript{2} expressed as a per cent of the CPET peak VO\textsubscript{2} (6MWT-VO\textsubscript{2}%) is shown in Figure 2A. The 6MWT-VO\textsubscript{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-VO\textsubscript{2} > 110% of the peak VO\textsubscript{2}, as shown in Figure 2B. Figure 2C shows the correlation between peak V\textsubscript{E} and 6MWT-V\textsubscript{E} expressed as the % of peak V\textsubscript{E} at CPET (6MWT-V\textsubscript{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 V\textsubscript{E} values obtained at CPET is reported in Figure 2D and 2F, respectively.

Figure 3 shows a correlation between peak VO\textsubscript{2} (upper panel) or 6MWT-VO\textsubscript{2} (lower panel) and distance walked during 6MWT in the entire study population. Moreover, the VO\textsubscript{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-VO\textsubscript{2} significantly correlates with 6MWT-VO\textsubscript{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-VO\textsubscript{2}% vs. 6MWT-VO\textsubscript{2} relationship progressively increased as exercise limitation did (Figure 4).

Regarding 6MWT results, the greater the exercise limitation severity, the lower were absolute 6MWT-V\textsubscript{E} and V\textsubscript{E}/VO\textsubscript{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 VO\textsubscript{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-VO\textsubscript{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 VO\textsubscript{2} achieved at CPET as the severity of HF becomes greater (Figure 2A and 2B).

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 VO\textsubscript{2} comparison between biking and walking efforts, we considered a +10% correction factor, as previously reported, being the oxygen uptake on the bike lower than the one observed during walking.

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\textsubscript{2} and VE/VO\textsubscript{2} slope have been found to be very prognostic also in elderly HF patients. A few previous reports addressed oxygen consumption in 6MWT. Holland et al. reported, in a study involving 47 patients with interstitial lung disease, that a significant proportion (45%) of subjects showed higher VO\textsubscript{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, V\textsubscript{E}, VO\textsubscript{2}, and SpO\textsubscript{2}.

As for 6MWT, V\textsubscript{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 VO\textsubscript{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 VO\textsubscript{2} and V\textsubscript{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 |
|------------------|---------|
|                  | VO₂ < 12| VO₂ 12–16 | VO₂ > 16 |
|                  | 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 VO₂ (mL/min) | 45 776  160 | 44 1030 201 | 26 1367 230 | <0.001 | <0.001 | <0.001 |
| Peak VO₂ (mL/kg/min) | 45 10.44 1.11 | 44 13.54 0.96 | 26 18.80 2.68 | <0.001 | <0.001 | <0.001 |
| VO₂/CO₂ slope | 44 40.9 10.4 | 44 38.1 8.7 | 26 31.6 5.3 | <0.001 | <0.001 | 0.410 |
| Peak Ve (L/min) | 45 39.5 9.6 | 44 47.4 12.2 | 26 59.0 11.6 | <0.001 | <0.001 | 0.003 |
| Peak RER | 45 1.09 0.14 | 44 1.06 0.08 | 26 1.11 0.11 | 0.732 | 0.224 |
| VO₂/work | 30 7.64 1.71 | 44 8.33 1.62 | 24 9.59 0.86 | <0.001 | <0.001 | 0.190 |
| 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 |
| Peak work (W) | 45 60 19 | 44 79 18 | 26 105 22 | <0.001 | <0.001 | 0.001 |
| 6 min walking test |         |           |          |           |          |           |            |        |          |          |          |
| Rest VO₂ 6MWT (L/min) | 45 519 128 | 44 513 139 | 26 482 161 | 0.320 | 0.545 |
| VO₂ 6MWT (mL/kg/min) | 45 835 225 | 44 975 267 | 26 1147 237 | <0.001 | <0.001 | 0.024 |
| VO₂ 6MWT (% peak VO₂) | 45 11.3 2.5 | 44 12.7 3.1 | 26 15.6 2.4 | <0.001 | <0.001 | 0.043 |
| Ve 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 |
| VCO₂/CO₂ 6MWT | 45 49.6 6.8 | 44 43.9 6.9 | 26 38.8 5.9 | <0.001 | <0.001 | 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 |
| PetO₂ 6MWT (mmHg) | 45 113.2 5.7 | 44 110.9 5.2 | 26 108.1 3.8 | <0.001 | 0.001 | 0.109 |
| PetCO₂ 6MWT (mmHg) | 45 28.3 3.4 | 44 30.7 4.1 | 26 34.4 3.7 | <0.001 | <0.001 | 0.008 |
| VCO₂ 6MWT (mL/min) | 45 655 181 | 44 767 204 | 26 897 199 | <0.001 | <0.001 | 0.023 |
| RER 6MWT | 45 1.1 0.14 | 44 1.05 0.16 | 26 1.02 0.09 | 0.004 | 0.013 | 0.089 |
| Distance 6MWT (m) | 44 340 88 | 44 405 72 | 26 449 76 | <0.001 | <0.001 | 0.001 |
| SpO₂ basal 6MWT (%) | 43 97 2 | 44 97 2 | 26 97 2 | 0.007 | 0.024 | 0.150 |
| SpO₂ stop 6MWT (%) | 43 95 3 | 44 96 2 | 26 97 2 | 0.007 | 0.024 | 0.150 |
| 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; PetCO₂, end-tidal carbon dioxide pressure; PetO₂, end-tidal oxygen pressure; RER, respiratory gas exchange; SpO₂, haemoglobin oxygen saturation; VCO₂, expired CO₂ volume; Ve, ventilation; VO₂, oxygen uptake; VT, tidal volume.
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 O₂ and CO₂ 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-V̇O₂, the greater is the use of aerobic metabolism if reported as a percentage of peak V̇O₂ at CPET (6MWT-V̇O₂%). Therefore, in patients with severe HF, even...
a small increase in 6MWT-VO₂ leads to an exhaustion of the aerobic metabolism possible in these cases, as shown by the steepness of the 6MWT-VO₂%/ vs. 6MWT-VO₂ 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. Of note, post-exercise acute pulmonary oedema is a possible consequence of maximal exercise in HF, albeit usually neglected as a direct consequence of it, as it appears sometime after the effort. SpO₂ 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 SpO₂ has been demonstrated at peak exercise in healthy subjects, but only in elite athletes. 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 SpO₂, which may not allow complete haemoglobin saturation at the level of some low efficiency alveolar/capillary units. Moreover, it is believed that in HF, a reduction of SpO₂ implies the presence of concomitant lung disease. The present study finding of a significant (although minor and not clinically relevant) SpO₂ 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. Indeed, Hb O₂ 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. Accordingly, to maintain SpO₂, the alveolar capillary pO₂ gradient must increase, which means further ventilation and work of breathing.
A few study limitations must be recognized. First, wearable K5 and stationary Quark differ for the CO2 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.

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Conflict of interest

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

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References

1. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardipulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211–277.
2. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, Coke LA, Fleg JL, Forman DR, Gerber TC, Gulati M, Madan K, Rhodes J, Thompson PD, Williams MA, American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013; 128: 873–934.
3. Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. Int J Cardiol 2019; 288: 107–113.
4. Gayda M, Temfemo A, Choquet D, Ahmadi S. Cardiorespiratory requirements and reproducibility of the six-minute walk test in elderly patients with coronary artery disease. Arch Phys Med Rehabil 2004; 85: 1538–1543.
5. Holland AE, Dowman L, Fiore J Jr, Brazzale D, Hill CJ, McDonald CF. Cardiorespiratory responses to 6-minute walk test in interstitial lung disease: not always a submaximal test. BMC Pulm Med 2014; 14: 136.
6. John M, Halle M, Schuster T, Hanssen H, Weis M, Koehler F, Schmidt-Thuksa A. The 6-min walk test in heart failure: is it a max or sub-maximum exercise test? Eur J Appl Physiol 2009; 107: 317–323.
7. Giannitsis S, Bougiakli M, Bechlioulis A, Kotsia A, Michalis IK, Naka KK. 6-minute walking test: a useful tool in the management of heart failure patients. *Ther Adv Cardiovasc Dis* 2019; 13: 175394719870084.

8. Agostoni P, Bianchi M, Moraschi A, Palermo P, Cattadori G, La Gioia R, Bussotti M, Wasserman K. Work-rate affects cardiopulmonary exercise testing in heart failure. *Eur J Heart Fail* 2005; 7: 498–504.

9. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.

10. Piepoli MF, Corra U, Agostoni PG, Belardinelli R, Cohen-Solal A, Hambrecht R, Vanhees L. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation part II: how to perform cardiopulmonary exercise testing in chronic heart failure. * Eur J Cardiovasc Prev Rehabil* 2006; 13: 300–311.

11. Agostoni P, Paolillo S, Mapelli M, Gentile P, Salvioni E, Veglia F, Bonomi P, Corra U, Lagioia R, Limongelli G, Sinagra G, Cattadori G, Scardovi AB, Metra M, Carubbia V, Scrutinio D, Raimondo R, Emdin M, Piepoli M, Magri D, Parati G, Caravita S, Re F, Cicoira M, Mina C, Correale M, Frigerio M, Bussotti M, Oliva F, Battaia E, Belardinelli R, Mezzani A, Pastormerlo L, Guazzi M. Does lung diffusion impair exercise testing in a population with high-risk cardiovascular diseases. *Circulation* 2012; 126: 2465–2472.

12. Venkatesh B, Janardhanan KG, Prasad S, Kataria P, Jha S, Barj S, Chauhan M, Datta S. Exercise-induced hypoxaemia in elite endurance athletes. Incidence, causes and impact on VO_{2max}. *Sports Med* 1993; 16: 14–22.

13. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Clinical exercise testing. In *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Lippincott Williams & Wilkins; 2005. p 137–138.

14. Perez-Suarez I, Martin-Rincon M, Gonzalez-Henriquez JJ, Pezzardi C, Perez-Regalado S, Galvan-Alvarez V, Juan-Habib JW, Morales-Alamo D, Calbet JAL. Accuracy and precision of the COSMED K5 portable analyser. *Front Physiol* 2018; 9: 1764.

15. Crouter SE, LaMunion SR, Hibbing PR, Kaplan AS, Bassett DR Jr. Accuracy of the Cosmed K5 portable gas exchange system in breath-by-breath mode. *PloS ONE* 2019; 14: e0226290.

16. Guidetti L, Meucci M, Bolletta F, Emerenziani GP, Gallotta MC, Balardi C. Validity, reliability and minimum detectable change of COSMED K5 portable gas exchange system in breath-by-breath mode. *PloS ONE* 2018; 13: e0209925.

17. Levinger I, Bronsks R, Cody DV, Linton I, Davie A. Perceived exertion as an exercise intensity indicator in chronic heart failure patients on beta-blockers. *J Sports Sci Med* 2004; 3: 23–27.

18. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, Agostoni PG. Lung function and exercise gas exchange in chronic heart failure. *Circulation* 1997; 96: 2221–2227.

19. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985; 132: 919–923.

20. Shepard RJ. Tests of maximum oxygen intake. A critical review. *Sports Med* 1984; 1: 99–124.

21. Hansen JE. Exercise instruments, schemes, and protocols for evaluating the dyspneic patient. *Am Rev Respir Dis* 1984; 129: S25–S27.

22. Meijhert M, Linder-Kingsell E, Ednner M, Kahan T, Persson H. Ventilatory variables are strong prognostic markers in elderly patients with heart failure. *Heart* 2002; 88: 239–243.

23. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. *Circulation* 2012; 126: 2465–2472.

24. Agostoni P, Cattadori G, Bianchi M, Wasserman K. Exercise-induced pulmonary edema in heart failure. *Circulation* 2003; 108: 2666–2671.

25. Powers SK, Martin D, Dodd S. Exercise-induced hypoxaemia in elite endurance athletes. Incidence, causes and impact on VO_{2max}. *Sports Med* 1993; 16: 14–22.

26. Agostoni P, Bussotti M, Cattadori G, Margutti E, Contini M, Muratori M, Marenzi G, Fiorentini C. Gas diffusion and alveolar-capillary unit in chronic heart failure. *Eur Heart J* 2006; 27: 2538–2543.

27. Clark AL, Coats AJ. Usefulness of arterial blood gas estimations during exercise in patients with chronic heart failure. *Br Heart J* 1994; 71: 528–530.

28. Agostoni PG, Bussotti M, Palermo P, Guazzi M. Does lung diffusion impairment affect exercise capacity in patients with heart failure? *Heart* 2002; 88: 453–459.

29. Morosini M, Vignati C, Novi A, Salvioni E, Veglia F, Alimenti M, Merli G, Sciomer S, Sinagra G, Agostoni P. The alveolar to arterial oxygen partial pressure difference is associated with pulmonary diffusing capacity in heart failure patients. *Respir Physiol Neurobiol* 2016; 233: 1–6.