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ORIGINAL RESEARCH ARTICLE

Exercise performance, haemodynamics, and respiratory pattern do not identify heart failure patients who end exercise with dyspnoea from those with fatigue†

Marco Morosin[1,2], Stefania Farina[1], Carlo Vignati[1], Emanuele Spadafora[1], Susanna Sciomer[3], Elisabetta Salvioni[1], Gianfranco Sinagra[2] and Piergiuseppe Agostoni[1,4]*

[1]*Centro Cardiologico Monzino, IRCCS, Milan, Italy;* [2]*Cardiovascular Department 'Ospedali Riuniti' Trieste and Postgraduate School Cardiovascular Sciences, University of Trieste, Trieste, Italy;* [3]*Department of Cardiovascular, Respiratory, Geriatric, Nephrology and Anesthesiology Sciences, Sapienza University of Rome, Rome, Italy; and* [4]*Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy*

Abstract

Aims The two main symptoms referred by chronic heart failure (HF) patients as the causes of exercise termination during maximal cardiopulmonary exercise testing (CPET) are muscular fatigue and dyspnoea. So far, a physiological explanation why some HF patients end exercise because of dyspnoea and others because of fatigue is not available. We assessed whether patients referring dyspnoea or muscular fatigue may be distinguished by different ventilator or haemodynamic behaviours during exercise.

Methods and results We analysed exercise data of 170 consecutive HF patients with reduced left ventricular ejection fraction in stable clinical condition. All patients underwent maximal CPET and a second maximal CPET with measurement of cardiac output by inert gas rebreathing at peak exercise. Thirty-eight (age 65.0 ± 11.1 years) and 132 (65.1 ± 11.4 years) patients terminated CPET because of dyspnoea and fatigue, respectively. Haemodynamic and cardiorespiratory parameters were the same in fatigue and dyspnoea patients. VO_2 was 10.4 ± 3.2 and 10.5 ± 3.3 mL/min/kg at the anaerobic threshold and 15.5 ± 4.8 and 15.4 ± 4.3 at peak, in fatigue and dyspnoea patients, respectively. In fatigue and dyspnoea patients, peak heart rate was 110 ± 22 and 114 ± 22 beats/min, and VE/VCO_2 and VO_2/work relationship slopes were 31.2 ± 6.8 and 30.6 ± 8.2 and 10.6 ± 4.2 and 11.4 ± 5.5 L/min/W, respectively. Peak cardiac output was 6.68 ± 2.51 and 6.21 ± 2.55 L/min (*P* = NS for all).

Conclusions In chronic HF patients in stable clinical condition, fatigue and dyspnoea as reasons of exercise termination do not highlight different ventilatory or haemodynamic patterns during effort.

Keywords Exercise performance; Heart failure; Fatigue; Dyspnoea

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**Correspondence to: Piergiuseppe Agostoni, MD, PhD, Centro Cardiologico Monzino, IRCCS, via Parea 4, 20138, Milan, Italy. Tel: 0039 02 58002586; Fax: +39 02 58002008. Email: piergiuseppe.agostoni@unimi.it*
†*The study was performed at Centro Cardiologico Monzino, IRCCS, Milan, Italy.*

Introduction

In apparently healthy subjects and in patients with suspected cardiac disease, self-reported exercise-induced dyspnoea has been shown to identify a subgroup of subjects at higher risk of cardiovascular death in several[1–3]—albeit not all—reports.[4] Muscular fatigue and dyspnoea are the two main symptoms that are referred by chronic heart failure (HF) patients as the cause of exercise limitation. However, the role of dyspnoea at peak exercise as associated with prognosis is presently unclear in this setting, as only few studies have evaluated this issue, and with contradictory results. Indeed, in a report by Chase *et al.*,[5] exercise dyspnoea has been linked to a poorer exercise performance and a higher risk of adverse cardiovascular events, while in the series of HF patients of Witte *et al.*,[6] no differences in peak VO_2

and prognosis were observed when comparing patients with and without dyspnoea as exercise limiting symptom.

The cause of exercise-induced dyspnoea in HF patients has also been studied, but a clear physiological explanation is not available. In their pioneering work, Wilson and Mancini[7] suggested that exercise dyspnoea in HF is due to increased respiratory muscle work mediated by excessive ventilation and decreased lung compliance. Moreover, Nanas *et al*.[8] reported a correlation between inspiratory capacity and wedge pressure, and both were associated with exercise performance. Differently, Russel *et al*.[9] were unable to show a correlation between dyspnoea and lung function at rest and during exercise in HF patients. According to the study by Nanas *et al*.,[8] we observed a strong correlation between pulmonary function and exercise performance and, after a therapeutic intervention, an improvement of both pulmonary function and exercise performance, but not of alveolar capillary membrane gas diffusion.[10–13] However, in all these studies,[8,10–12] no correlation was reported between lung function abnormalities and exercise dyspnoea. So even at present, the reason why some HF patients end their exercise performance because of dyspnoea and other because of fatigue is basically unknown.[14] Accordingly, we analysed whether patients referring dyspnoea or fatigue as the cause of exercise limitation are characterized by a different ventilatory or haemodynamic behaviour during exercise. Specifically, we studied the behaviour of exercise performance, ventilatory pattern, and cardiac output (CO) in 170 consecutive HF patients who performed a maximal standard cardiopulmonary exercise testing (CPET) and a second maximal CPET to measure CO (CPET-CO) at rest and at peak exercise by inert gas rebreathing (IGR).

Methods

Patient population

We retrospectively analysed the clinical data, obtained as part of the routine HF follow-up program, of 170 consecutive patients (146 men and 24 women) who underwent full clinical evaluation at our HF unit. All patients underwent both CPET and CPET-CO within 2 months (16 ± 15 days). Patients belong to a cohort of HF patients regularly followed up at our HF unit. All were in stable clinical condition, in New York Heart Association (NYHA) functional class I–III, capable of performing standard CPET and rebreathing manoeuvres.

We excluded from data analysis HF patients with preserved left ventricular ejection fraction (LVEF) (>50% at echocardiography), and patients with primary pulmonary hypertension and pulmonary embolism or any disease, which per se influenced their exercise capacity.

Heart failure aetiology was as follows: ischaemic heart disease (35 patients), idiopathic cardiomyopathy (114 patients) and valvular heart disease (21 patients).

For the present analysis, we evaluated NYHA class, resting haemoglobin, brain natriuretic peptide, conventional two-dimensional and Doppler echocardiography, standard spirometry, CPET, and CPET-CO. Spirometry was performed according to current guidelines with a mass flow-meter (SensorMedics, Yorba Linda, CA, USA).[15] Predicted values were calculated according to Quanjer *et al*.[16]

Cardiopulmonary exercise testing

A maximal CPET was performed (229D Spectra metabolic cart, SensorMedics) on a cycle ergometer in patients without contraindications to the test (Erg 800S, SensorMedics), using a personalized ramp protocol aimed at achieving peak exercise in around 10 min. The majority of these patients had previously undergone a CPET in our laboratory; the other patients underwent a familiarization procedure. We analysed CPET using a standard methodology. All CPETs were performed by a cardiology expert on CPET, a fellow, and a dedicated nurse. CPET was self-interrupted by the patients when he or she claimed that he or she had reached a maximal effort. We systematically asked the patients the reason why the procedure was terminated and if it was specifically because of chest pain, dyspnoea, or fatigue. Peak VO_2 was calculated as an average over 30 s and reported either as absolute value or as a percentage of the VO_2 max predicted value.[17] The O_2 pulse was calculated as VO_2/heart rate (HR). The VO_2/work relationship was calculated through the entire exercise, while the ventilation (VE)/carbon dioxide flow (VCO_2) slope was calculated as the slope of the relationship between VE and VCO_2 from approximately 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period.[18]

A CPET-CO was performed using the same ramp protocol of CPET. CO was measured at rest and at peak exercise using an IGR method[19–21] that required a few teaching sessions to familiarize patients with the necessary manoeuvre. The IGR technique has been previously reported in detail.[19] In brief, the IGR technique uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulfur hexafluoride) inflated into a bag by the machine. Patients have to breathe into a respiratory valve via a mouthpiece and a bacterial filter with a nose clip. At the end of expiration, the valve is activated automatically so that patients rebreathe from the prefilled bag for a period of 10 to 20 s. After that period, patients start breathing ambient air again. CO measurement is performed by a photo-acoustic analyser that measures gas concentration over a five-breath interval. Sulfur hexafluoride, which is insoluble in blood, is used to determine lung volume, while the concentration of nitrous oxide, which is soluble in blood, decreases during rebreathing with a rate that is proportional to pulmonary blood flow. CO is equal to pulmonary blood flow only if the arterial oxygen saturation (SpO_2) measure is >98% at pulse oximeter, showing

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the absence of pulmonary shunt flow. If SpO_2 is <98%, CO is equal to pulmonary blood flow plus shunt flow.[19] In CPET-CO, respiratory gases and ventilation were measured breath by breath as in CPET.

Arterio-venous O_2 content differences [ΔCO_2(a-v)] was calculated as VO_2/CO.

Both CPETs were performed as part of the clinical evaluation that we routinely perform at our HF unit. We obtained written informed consent before each CPET for the exercise procedure as well as for the blind research use of CPET derived data as well as for all patients' clinical data. The present retrospective study was reviewed and approved by our institutional review board (Centro Cardiologico Monzino ethics committee) before the study began.

Statistical analysis

Continuous variables were expressed as means ± standard deviation, or as median and interquartile range if not normally distributed. Comparisons between the two groups were performed using unpaired *t*-tests for normally distributed variables, and Mann–Whitney *U*-test for non-normally distributed variables. $P < 0.05$ was considered statistically significant.

Statistical analysis was performed using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA).

Results

We studied a cohort of 170 patients in NYHA class I, *n* = 42 (25%); II, *n* = 93 (55%); and III, *n* = 35 (20%). Patients' age was 65 ± 11 years, and 86% were male. Average LVEF was 31 ± 8%. Spirometry showed forced expiratory volume in 1 s is equal to 82.8 ± 18.0% of the predicted value and forced vital capacity equal to 88.2 ± 16.9% of the predicted value. Thirty-eight patients terminated the CPET procedure because of dyspnoea, and 132 because of muscular fatigue. The mean ramp protocol used was 9.03 ± 3.3 W/min in both exercise tests. The duration of the tests was 9.3 ± 1.7 and 9.1 ± 2.7 min (average work rate = 83.4 ± 33.4 W) in CPET and CPET-CO, respectively. Peak exercise respiratory gas exchange was 1.14 ± 0.11 in CPET, showing that, on average, patients performed a maximal or nearly maximal exercise test in both CPETs.

The cardiorespiratory performance was analysed during CPET to avoid any possible interference of the rebreathing manoeuvre with ventilation and respiratory gases. The anaerobic threshold was identified in 94% of patients. At anaerobic threshold, VO_2 was 0.80 ± 0.29 L/min (10.2 ± 3.2 mL/kg/min), HR was 90 ± 16 beats/min, and end-tidal pCO_2 was 35.1 ± 4.1 mmHg. At peak exercise, VO_2 was 1.2 ± 0.4 L/min corresponding to 15.5 ± 4.7 mL/kg/min and to 61.8 ± 18.4% of the predicted value; HR was 111 ± 22 beats/min; and oxygen pulse was 11.4 ± 5.7 mL/min. The slopes of VE/VCO_2 and VO_2/work relationship were 31.1 ± 7.1 and 10.8 ± 4.6 L/min/W, respectively.

Patients were grouped according to the reason (muscular fatigue or dyspnoea) that led them to terminate the procedure (*Table 1*). No difference was observed in terms of all analysed parameters derived from CPET and CPET-CO (*Table 2*). Patients' data were included in the MECKI score dataset.[22] Cardiovascular mortality was low at 1 year (only two cases in the muscular fatigue group), confirming that patients were in stable clinical condition and optimized drug treatment.

Discussion

The main finding of the present study is that 22% of patients ended the effort because of dyspnoea and 78% because of fatigue. Patients ending a maximal effort because of dyspnoea had the same peak VO_2, peak HR, peak CO, ΔCO_2(a-v), and VE/VCO_2 slope as those ending their exercise because of fatigue.

We analysed data of HF patients in stable clinical conditions who performed two CPETs and excluded those who performed

Table 1 General characteristics of patients who interrupted exercise because of muscular fatigue and those who did because of dyspnoea

Variables	Muscular fatigue (*n* = 132)	Dyspnea (*n* = 38)	*P* value
Age, years	65 ± 11.1	65.1 ± 11.4	0.93
Gender (male), *n*	87%	82%	0.27
BMI, kg/m^2	26.4 ± 4.3	26.1 ± 3.9	0.67
NYHA class I	25%	24%	0.86
NYHA class II	55%	53%	
NYHA class III	20%	23%	
Haemoglobin, g/dL	14.0 (12.7–14.8)	14.1 (13.0–14.7)	0.97
BNP, pg/mL	221 (79–577)	414 (251–745)	0.58
LVEF, %	31.3 ± 8	31.4 ± 8	0.94
LVeSV, mL	147 ± 66	134 ± 48	0.29
LVeDV, mL	209 ± 80	191 ± 52	0.22
PAPs, mmHg	34.4 ± 12.2	34.8 ± 13.5	0.89
Beta-blockers, *n*	93%	87%	0.26
ACE inhibitors, *n*	70%	65%	0.35
ARBs, *n*	18%	23%	0.34
Diuretics, *n*	78%	81%	0.46
Antialdosteronic drug, *n*	58%	71%	0.14
Digitalis, *n*	4%	3%	0.64
FEV1, % of predicted	82.3 ± 17.9	84.1 ± 18.4	0.65
FVC, % of predicted	87.7 ± 16.7	89.8 ± 17.7	0.58

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVeDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVeSV, left ventricular end-systolic volume; NYHA, New York Heart Association; PAPs, pulmonary artery systolic pressure.
Patients were grouped according to the reason (muscular fatigue or dyspnoea) that led them to terminate the procedure. No difference was observed in terms of all analysed parameters. Data are expressed as mean ± standard deviation or as median (25th–75th quartile).

Table 2 Difference of exercise parameters between patients who interrupted exercise because of muscular fatigue and those who did because of dyspnoea

Variables	Muscular fatigue (n = 132)	Dyspnoea (n = 38)	P value
Ramp protocol	10 (6–12)	8 (6–10)	0.13
Test length, min	9.22 ± 1.72	9.68 ± 1.80	0.19
Achievement of AT, %	94	95	0.85
VO_2 at AT, L/min	0.82 ± 0.29	0.81 ± 0.30	0.91
VO_2 at AT, mL/kg/min	10.4 ± 3.2	10.5 ± 3.3	0.59
HR at AT, beats/min	89 ± 15.1	93 ± 17	0.19
Work at AT, W	48.9 ± 21.7	48.7 ± 24.8	0.98
Peak VO_2, L/min	1.21 ± 0.43	1.14 ± 0.41	0.38
Peak VO_2, mL/kg/min	15.49 ± 4.77	15.35 ± 4.34	0.87
Peak VO_2, % of predicted	61.8 ± 18.6	62.1 ± 19.7	0.88
Peak HR, beats/min	110 ± 22	114 ± 22	0.30
Peak HR, % of predicted	72 ± 13.4	74.7 ± 14.2	0.28
Work at peak, W	84.5 ± 33.2	79.6 ± 34.3	0.43
Peak O_2 pulse, mL/beat	11.8 ± 6.2	10.2 ± 3	0.12
VE/VCO_2 slope	31.2 ± 6.8	30.6 ± 8.2	0.65
Peak $PetCO_2$, mmHg	32.4 ± 4.7	31.3 ± 4.5	0.20
Y intercept, L/min	3.73 ± 2.33	4.11 ± 3.23	0.47
VO_2/work slope, L/min/W	10.6 ± 4.2	11.4 ± 5.5	0.34
Peak Vt, L	1.7 ± 0.5	1.7 ± 0.6	0.87
Peak VE, L	52.5 ± 16.7	51.7 ± 15.5	0.81
Breathing reserve, %	42.3 ± 15.3	43 ± 15.8	0.83
Respiratory rate, breath/min	31.4 ± 7.5	31.1 ± 7.2	0.78
RER	1.14 ± 0.11	1.14 ± 0.10	0.87
Baseline CO, L/min	3.26 ± 0.98	3.12 ± 0.92	0.43
Peak CO, L/min	6.68 ± 2.51	6.21 ± 2.55	0.32
Peak CO, % of predicted	51.6 ± 14.7	49.4 ± 16.9	0.44
Baseline SV, L/min	48.5 ± 15.1	46.6 ± 14	0.48
Peak SV, L/min	64.5 ± 21.2	58.3 ± 16.2	0.10
Peak SV, % of predicted	78.2 ± 21.6	74.5 ± 19.6	0.36
Baseline ΔCO_2(a-v), mL/100 mL	9.87 ± 3.2	10.1 ± 2.7	0.74
Peak ΔCO_2(a-v), mL/100 mL	18.2 ± 3.8	18.2 ± 3.6	0.98
Peak ΔCO_2(a-v), % of predicted	120 ± 26.8	123 ± 27.9	0.65

AT, anaerobic threshold; CO, cardiac output; HR, heart rate; Pet, pressure end-tidal; RER, respiratory gas exchange ratio; SV, stroke volume; VE, minute ventilation; VE/VCO_2, ventilatory efficiency; VO_2, oxygen uptake; Vt, tidal volume; ΔCO_2(a-v), arterio-venous oxygen difference.
Patients were grouped according to the reason (muscular fatigue or dyspnoea) that led them to terminate the procedure. No difference was observed in terms of all analysed parameters. Data are expressed as mean ± standard deviation or as median (25th–75th quartile).

only CPET-CO or with a time lag between the two tests >2 months. The first test was used to assess the metabolic parameters during exercise and the cause of exercise termination; the second one, CPET-CO, to measure CO by IGR. We chose this dual investigational strategy to avoid any possible interference of the rebreathing manoeuvre with the exercise performance and the sensation of dyspnoea. Indeed, we feared that the rebreathing manoeuvre, which requires an inspiration followed by five regular breaths at a fixed rate (usually 30 breath/min at peak exercise), might generate dyspnoea and somehow affect exercise performance. As a matter of fact, exercise tolerance was the same at both tests.

The percent of HF patients referring dyspnoea as the cause of exercise limitation varies among studies.[6,9,23] In the present study, we observed that the first cause for self-ending a maximal effort referred by patients with chronic HF is fatigue (78% of cases), and dyspnoea was reported in 22% of cases. It should be noticed that our patients belong to a cohort HF regularly followed up at our HF unit, who were all in stable clinical condition and on optimal treatment; and, consequently, fluid balance was likely optimal, and that almost all had had previous experience of CPET in our laboratory, likely reducing test-induced anxiety, which is more likely associated with dyspnoea.

Patients referring dyspnoea as the cause of exercise termination showed, at peak exercise and at the anaerobic threshold, data similar to those recorded in patients who referred fatigue as the cause of exercise limitation. Also the VO_2/work relationship, an index of the efficiency of O_2 delivery to the periphery, was similar. This datum, combined with direct CO measurement and calculated ΔCO_2(a-v), reinforces the concept of a similar haemodynamic behaviour during exercise. Moreover, the symptom referred by the patients as the cause of exercise termination was unrelated to HF severity or characteristics as evaluated by NYHA class, LVEF, haemoglobin concentration, or peak VO_2.

It is of note that neither resting spirometry nor ventilatory parameters during exercise were able to differentiate patients who stopped exercise because of dyspnoea from those who stopped because of fatigue. In particular, neither the VE/VCO_2 slope, a parameter of ventilatory efficiency known to increase in case of pulmonary hypertension, nor the VE intercept of the VE/VCO_2 relationship, which increases in case of respiratory co-morbidities in HF patients, was different.[24] It is therefore likely that the different symptoms referred are related to the individually built central reconstruction of similar peripheral signals, making impossible for the patients to differentiate between dyspnoea and fatigue or between central and peripheral exercise ending causes.

A few study limitations should be acknowledged. First of all, we have not tested the repeatability of the symptom referred as the cause of exercise termination by the patients. Similarly, in the present setting of patients, repeatability of peak CO was not tested, albeit IGR precision and repeatability have been previously shown.[19–21] Finally neither a Borg dyspnoea scale nor Borg Rating of Perceived Exertion scale was obtained at the end of each CPET.

In conclusion, in chronic HF patients in stable clinical condition and on optimal treatment, fatigue and dyspnoea as causes of exercise termination during self-interrupted CPET do not underscore different cardiorespiratory or haemodynamic patterns.

Conflict of interest

None declared.

References

1. Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul-Enein F, Cohen I, Friedman JD, Germano G, Berman DS. Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med* 2005; **353**: 1889–1898.
2. Argulian E, Agarwal V, Bangalore S, Chatterjee S, Makani H, Rozanski A, Chaudhry FA. Meta-analysis of prognostic implications of dyspnea versus chest pain in patients referred for stress testing. *Am J Cardiol* 2014; **113**: 559–564.
3. Bodegard J, Erikssen G, Bjornholt JV, Gjesdal K, Liestol K, Erikssen J. Reasons for terminating an exercise test provide independent prognostic information: 2014 apparently healthy men followed for 26 years. *Eur Heart J* 2005; **26**: 1394–1401.
4. Jones LW, Devlin SM, Maloy MA, Wood WA, Tuohy S, Espiritu N, Aquino J, Kendig T, Michalski MG, Gyurkocza B, Schaffer WL, Ali B, Giralt S, Jakubowski AA. Prognostic importance of pretransplant functional capacity after allogeneic hematopoietic cell transplantation. *Oncologist* 2015; **20**: 1290–1297.
5. Chase P, Arena R, Myers J, Abella J, Peberdy MA, Guazzi M, Kenjale A, Bensimhon D. Prognostic usefulness of dyspnea versus fatigue as reason for exercise test termination in patients with heart failure. *Am J Cardiol* 2008; **102**: 879–882.
6. Witte KK, Clark AL. Dyspnoea versus fatigue: additional prognostic information from symptoms in chronic heart failure? *Eur J Heart Fail* 2008; **10**: 1224–1228.
7. Wilson JR, Mancini DM. Factors contributing to the exercise limitation of heart failure. *J Am Coll Cardiol* 1993; **22**: 93A–98A.
8. Nanas S, Nanas J, Papazachou O, Kassiotis C, Papamichalopoulos A, Milic-Emili J, Roussos C. Resting lung function and hemodynamic parameters as predictors of exercise capacity in patients with chronic heart failure. *Chest* 2003; **123**: 1386–1393.
9. Russell SD, McNeer FR, Higginbotham MB. Exertional dyspnea in heart failure: a symptom unrelated to pulmonary function at rest or during exercise. Duke University Clinical Cardiology Studies (DUCCS) Exercise Group. *Am Heart J* 1998; **135**: 398–405.
10. Agostoni PG, Guazzi M, Bussotti M, Grazi M, Palermo P, Marenzi G. Lack of improvement of lung diffusing capacity following fluid withdrawal by ultrafiltration in chronic heart failure. *J Am Coll Cardiol* 2000; **36**: 1600–1604.
11. Agostoni PG, Marenzi GC, Pepi M, Doria E, Salvioni A, Perego G, Lauri G, Giraldi F, Grazi S, Guazzi MD. Isolated ultrafiltration in moderate congestive heart failure. *J Am Coll Cardiol* 1993; **21**: 424–431.
12. Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M, Cattadori G, Palermo P. Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J* 2005; **26**: 159–164.
13. 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.
14. Corra U, Piepoli MF, Adamopoulos S, Agostoni P, Coats AJ, Conraads V, Lambrinou E, Pieske B, Piotrowicz E, Schmid JP, Seferovic PM, Anker SD, Filippatos G, Ponikowski PP. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the committee on exercise physiology and training of the heart failure association of the esc. *Eur J Heart Fail* 2014; **16**: 929–941.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005; **26**: 319–338.
16. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; **16**: 5–40.
17. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; **129**: S49–S55.
18. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Clinical Exercise Testing. Principles of Exercise Testing and Interpretation including Pathophysiology and Clinical Applications*. Philadelphia: Lippincott Williams & Wilkins; 2005.
19. Cattadori G, Schmid JP, Agostoni P. Noninvasive measurement of cardiac output during exercise by inert gas rebreathing technique. *Heart Fail Clin* 2009; **5**: 209–215.
20. Agostoni P, Cattadori G, Apostolo A, Contini M, Palermo P, Marenzi G, Wasserman K. Noninvasive measurement of cardiac output during exercise by inert gas rebreathing technique: a new tool for heart failure evaluation. *J Am Coll Cardiol* 2005; **46**: 1779–1781.
21. Gabrielsen A, Videbaek R, Schou M, Damgaard M, Kastrup J, Norsk P. Noninvasive measurement of cardiac output in heart failure patients using a new foreign gas rebreathing technique. *Clin Sci (Lond)* 2002; **102**: 247–252.
22. Agostoni P, Corra U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magri D, Fiorentini C, Mezzani A, Salvioni E, Scrutinio D, Ricci R, Bettari L, Di Lenarda A, Pastormerlo LE, Pacileo G, Vaninetti R, Apostolo A, Iorio A, Paolillo S, Palermo P, Contini M, Confalonieri M, Giannuzzi P, Passantino A, Cas LD, Piepoli MF, Passino C. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013; **167**: 2710–2718.
23. Piepoli MF, Guazzi M, Boriani G, Cicoira M, Corra U, Dalla Libera L, Emdin M, Mele D, Passino C, Vescovo G, Vigorito C, Villani GQ, Agostoni P. Exercise intolerance in chronic heart failure: mechanisms and therapies. Part I. *European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2010; **17**: 637–642.
24. Apostolo A, Laveneziana P, Palange P, Agalbato C, Molle R, Popovic D, Bussotti M, Internullo M, Sciomer S, Bonini M, Alencar MC, Godinas L, Arbex F, Garcia G, Neder JA, Agostoni P. Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. *Int J Cardiol* 2015; **189**: 134–140.