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

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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. VO2 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/VCO2 and VO2/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

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 several1–3—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 VO2...
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 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. reported a correlation between inspiratory capacity and wedge pressure, and both were associated with exercise performance. Differently, Russel et al. 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., 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. However, in all these studies, 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. 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). Predicted values were calculated according to Quanjer et al.

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 VO2 was calculated as an average over 30 s and reported either as absolute value or as a percentage of the VO2 max predicted value. The O2 pulse was calculated as VO2/heart rate (HR). The VO2/work relationship was calculated through the entire exercise, while the ventilation (VE)/carbon dioxide flow (VCO2) slope was calculated as the slope of the relationship between VE and VCO2 from approximately 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period.

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 that required a few teaching sessions to familiarize patients with the necessary manoeuvre. The IGR technique has been previously reported in detail. 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 (SpO2) measure is >98% at pulse oximeter, showing...
the absence of pulmonary shunt flow. If SpO2 is < 98%, CO is equal to pulmonary blood flow plus shunt flow. In CPET-CO, respiratory gases and ventilation were measured breath by breath as in CPET.

Arterio-venous O2 content differences [ΔCO2(a-v)] was calculated as VO2/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 9.2 ± 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, VO2 was 0.80 ± 0.29 L/min (10.2 ± 3.2 mL/kg/min), HR was 90 ± 16 beats/min, and end-tidal pCO2 was 35.1 ± 4.1 mmHg. At peak exercise, VO2 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/VCO2 and VO2/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. 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 VO2, peak HR, peak CO, ΔCO2(a-v), and VE/VCO2 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) | Dyspnoea (n = 38) | P value |
| Age, years              | 65 ± 11.1                    | 65.1 ± 11.4      | 0.93    |
| Gender (male), n         | 87%                          | 82%              | 0.27    |
| BMI, kg/m²               | 26.4 ± 4.3                   | 26.1 ± 3.9       | 0.67    |
| NYHA class I             | 25%                          | 24%              |         |
| NYHA class II            | 55%                          | 53%              | -0.86   |
| 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    |
| LVEFV, 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; LVEFV, 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 breath/min) | 9.2 ± 1.72 | 9.68 ± 1.80 | 0.19 |
| Ve at AT, L/min                  | 94                          | 95                | 0.85 |
| VCO₂ 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 VO₂, L/min                  | 52.5 ± 16.7          | 51.7 ± 15.5       | 0.81 |
| Peak VE, L                       | 1.7 ± 0.5               | 1.7 ± 0.6        | 0.87 |
| ΔBaseline Peak CO, % of predicted| 72 ± 3.4               | 74.7 ± 14.2      | 0.28 |
| ΔBaseline CO, L/min              | 84.5 ± 32.2          | 79.8 ± 34.3       | 0.43 |
| Peak CO₂ slope                   | 31.2 ± 6.8            | 30.6 ± 8.2        | 0.65 |
| Peak PetCO₂, mmHg                | 32.4 ± 4.7            | 31.3 ± 4.5        | 0.20 |
| Y intercept, L/min               | 3.73 ± 2.33          | 4.11 ± 3.33       | 0.47 |
| VCO₂/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 |
| Peak V̇CO₂, L/min                | 48.5 ± 15.1          | 46.6 ± 14         | 0.48 |
| Peak V̇CO₂, % of predicted       | 64.5 ± 21.2          | 58.3 ± 16.2       | 0.10 |
| Baseline ΔCO₂(a-v), mL/100 mL    | 8.97 ± 3.2           | 10.1 ± 2.7        | 0.74 |
| Peak ΔCO₂(a-v), mL/100 mL        | 18.2 ± 3.8           | 18.2 ± 3.6        | 0.98 |
| Peak ΔCO₂(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/VCO₂, ventilatory efficiency; VO₂, oxygen uptake; Vt, tidal volume; ΔCO₂(a-v), arterio-venous oxygen difference.

The percent of HF patients referring dyspnoea as the cause of exercise limitation varies among studies. 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 VO₂/work relationship, an index of the efficiency of O₂ delivery to the periphery, was similar. This datum, combined with direct CO measurement and calculated ΔCO₂(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 VO₂.

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/VCO₂ slope, a parameter of ventilatory efficiency known to increase in case of pulmonary hypertension, nor the VE intercept of the VE/VCO₂ relationship, which increases in case of respiratory co-morbidities in HF patients, was different.

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.

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, Germaino 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. Bodgardi J, Eriksen G, Bjornholt JV, Gjesdal K, Lieotl K, Eriksen 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, Pedersen OF, Pellegrino R, Viegi G, MacIntyre N, McKay R, Navajas D, Gao W, Verma A, Shouler J, Schuster J, Emmons CR, Beghetti M. Exertional dyspnea in heart failure: mechanisms and therapies. Circulation 2013; 127: e224–e246.

5. Lambrinou E, Pieske B, Piotrowicz E, Margutti E, Contini M, Muratori M, Marenzi G, Fiorentini C. Gas diffusion in heart failure patients using a new foreign gas rebreathing technique. J Am Coll Cardiol 2008; 51: 1028–1035.

6. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Wasserman K. Predicted values for clinical exercise testing. Am Rev Respir Dis 1984; 129: S49–S55.

7. 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.

8. Agostoni P, Magini A, Andreini D, Bodegard J, Erikssen G, Bjornholt JV, Gjesdal K, Lieotl K, Eriksen J. Lack of improvement of lung diffusing capacity following fluid withdrawal by ultrafiltration in chronic heart failure. J Am Coll Cardiol 2000; 36: 1600–1604.

9. Agostoni P, Marenzi GC, Pepi M, Doria F, Salvioni A, Perego G, Lauri G, Giraldi F, Grazi S, Guazzi MD. Isolated ultrafiltration improves lung diffusion in chronic heart failure. J Am Coll Cardiol 1993; 21: 424–431.

10. 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.

11. 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.

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, 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.

14. Corra U, Piepoli MF, Adamopoulos S, Agostoni P, Coats AJ, Conraads V, Lambrinou E, Pieske B, Piotrowicz E, Scrutinio D, Ricci R, Bettari I, 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.

15. Piepoli MF, Guazzi M, Boriani G, Cicoira M, Corra U, Dalla Libera L, Emdin M, Mele D, Passino C, Vecchietti G, Vigorito C, Villani GQ, Agostoni P. Exercise intolerance in chronic heart failure: mechanisms and therapies. Part 1. 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.

16. Apostolo A, Laveneziana P, Palange P, Agabato C, Molle R, Popovic D, Bussotti M, Internullo M, Scimer S, Bonini M, Alencar MC, Godinas I, Arbex F, Garcia N, Neder JA, Agostoni P. Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. Int J Cardiol 2015; 189: 134–140.

17. AGUSTONI P, SCHMID JP, AGOSTONI P. Non-invasive measurement of cardiac output during exercise by inert gas rebreathing technique. Heart Fail Clin 2009; 5: 209–215.

18. AGOSTONI P, CATTADORI G, APPOSTO A, CONTINI M, PALERMO P, MARENZI G, WASSEMER K. Non-invasive 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.

19. Gabrielsen A, Videbaek R, Schou M, Damgaard M, Kastrup J, Norsk P. Non-invasive measurement of cardiac output in heart failure patients using a new foreign gas rebreathing technique. Clin Sci (Lond) 2002; 102: 247–252.

20. 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 I, 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.

21. Piepoli MF, Guazzi M, Boriani G, Cicoira M, Corra U, Dalla Libera L, Emdin M, Mele D, Passino C, Vecchietti G, Vigorito C, Villani GQ, Agostoni P. Exercise intolerance in chronic heart failure: mechanisms and therapies. Part 1. 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.

22. Apostolo A, Laveneziana P, Palange P, Agabato C, Molle R, Popovic D, Bussotti M, Internullo M, Scimer S, Bonini M, Alencar MC, Godinas I, Arbex F, Garcia N, Neder JA, Agostoni P. Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. Int J Cardiol 2015; 189: 134–140.