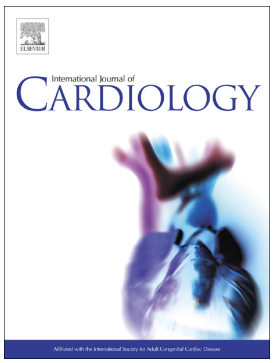

Influence of exertional oscillatory breathing and its temporal behavior in patients with heart failure and reduced ejection fraction

Damiano Magrì, Pietro Palermo, Elisabetta Salvioni, Massimo Mapelli, Giovanna Gallo, Carlo Vignati, Irene Mattavelli, Paola Gugliandolo, Antonello Maruotti, Pierfrancesco Alaimo Di Loro, Emiliano Fiori, Susanna Sciomer, Piergiuseppe Agostoni

PII: S0167-5273(23)00659-9

DOI: https://doi.org/10.1016/j.ijcard.2023.05.008

Reference: IJCA 31058

To appear in: *International Journal of Cardiology*

Received date: 15 February 2023

Revised date: 12 April 2023

Accepted date: 5 May 2023

Please cite this article as: D. Magrì, P. Palermo, E. Salvioni, et al., Influence of exertional oscillatory breathing and its temporal behavior in patients with heart failure and reduced ejection fraction, *International Journal of Cardiology* (2023), https://doi.org/10.1016/j.ijcard.2023.05.008

Influence of exertional oscillatory breathing and its temporal behaviour in patients with heart failure and reduced ejection fraction.

Damiano Magrì[1*], MD, PhD, Pietro Palermo[2*], MD, Elisabetta Salvioni[2], PhD, Massimo Mapelli[2,3], MD, Giovanna Gallo[1], MD, PhD, Carlo Vignati[2], MD, Irene Mattavelli[2], PhD, Paola Gugliandolo[2], MD, Antonello Maruotti[4,5,6], PhD, Pierfrancesco Alaimo Di Loro[4], PhD, Emiliano Fiori[1], MD, Susanna Sciomer[7], MD, Piergiuseppe Agostoni[2,3], MD, PhD.

Affiliations:

[1] Department of Clinical and Molecular Medicine, Azienda Ospedaliera Sant'Andrea, "Sapienza" University, Rome, Italy.

[2] Centro Cardiologico Monzino, IRCCS, Milan, Italy.

[3] Dept. of Clinical sciences and Community health, Cardiovascular Section, University of Milano, Milan, Italy.

[4] Dipartimento di Giurisprudenza, Economia, Politica e Lingue Moderne - Libera Università Maria Ss Assunta

[5] Department of Mathematics, University of Bergen, Norway

[6] School of Computing, University of Portsmouth, United Kingdom

[7] Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, "Sapienza" University, Rome, Italy.

Running Title: EOV clinical implications in HFrEF patients

*Both share the first author privileges.

Total word count of the manuscript: 5864 (including references, tables and figure legends)

Correspondence to:

Piergiuseppe Agostoni, MD, PhD

Centro Cardiologico Monzino, IRCCS

Via Parea 4, 20138, Milan, Italy

Phone: 0039 02 58002586 - Fax 0039 02 58002283

E mail: piergiuseppe.agostoni@unimi.it

ABSTRACT

Background–Exertional oscillatory breathing (EOV) represents an emerging prognostic marker in heart failure (HF) patients, however little is known about EOV meaning with respect to its disappearance/persistence during cardiopulmonary exercise test (CPET). The present single-center study evaluated EOV clinical and prognostic impact in a large cohort of reduced ejection fraction HF patients (HFrEF) and, contextually, if a specific EOV temporal behavior might be an addictive risk predictor.

Methods and Results–Data from 1.866 HFrEF patients on optimized medical therapy were analysed. The primary cardiovascular (CV) study end-point was cardiovascular death, heart transplantation or LV assistance device (LVAD) implantation at 5-years. For completeness a secondary end-point of total mortality at 5- years was also explored. EOV presence was identified in 251 patients (13%): 142 characterized by EOV early cessation (Group A) and 109 by EOV persistence during the whole CPET (Group B). The entire EOV Group showed worse clinical and functional status than NoEOV Group (n=1.615) and, within the EOV Group, Group B was characterized by a more severe HF. At CV survival analysis, EOV patients showed a poorer outcome than the NoEOV Group (events 27.1% versus 13.1%, p<0.001) both unpolished and after matching for main confounders. Instead, no significant differences were found between EOV Group A and B with respect to CV outcome. Conversely the analysis for total mortality failed to be significant.

Conclusions–Our analysis, albeit retrospective, supports the inclusion of EOV into a CPET-centered clinical and prognostic evaluation of the HFrEF patients. EOV characterizes *per se* a more advanced HFrEF stage with an unfavorable CV outcome. However, the EOV persistence, albeit suggestive of a more severe HF, does not emerge as a further prognostic marker.

Key-words: heart failure; oscillatory exertional breathing; cardiopulmonary exercise testing; prognosis.

INTRODUCTION

Data coming from the analysis of ventilation (VE) by means of a maximal cardiopulmonary exercise test (CPET) have gained growing interest in patients with heart failure and reduced ejection fraction (HFrEF) [1-3]. In such a context, the relationship between VE and carbon dioxide (CO_2) production (VE/VCO_2 slope) and exertional oscillatory ventilation (EOV) represent the most remarkable variables. Indeed, VE/VCO_2 slope has been demonstrated a strong independent outcome predictor in HFrEF [4,5] and, notably, it has been included into the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) score, the most performing HF multiparametric prognostic model [6-8]. Conversely, EOV clinical and prognostic meaning still remains understated despite the large body of evidence supporting the EOV identification as a useful marker of mortality and morbidity in many different HF settings [9-13]. EOV is described as a slow, prominent, and nonrandom cyclic fluctuation of both VE and expired gas kinetics, however several definition criteria have been proposed [14,15]. At present, the American Heart Association suggests the use of Corrà et al. definition [16,17] but a standardized and easy to apply definition is still lacking but highly desirable [18]. Of note, some EOV specific patterns are still not considered regardless of the EOV definition applied. Specifically, it is unknown whether EOV disappearance/persistence during the entire CPET execution has independent role as regards grading of HF severity and prognosis [19].

Aim of the present single-center retrospective study was to evaluate the prognostic impact of EOV in a large cohort of stable HFrEF patients on optimized treatment and, possibly, to identify if the EOV behavior during the whole exercise (i.e. early cessation/persistence) might act as a further information to better define HF severity and mortality.

METHODS

- Study Sample

The initial study cohort consisted of 1.866 consecutive stable patients with HFrEF secondary to dilated post-ischaemic or idiopathic cardiomyopathy who underwent a full clinical assessment, including a maximal CPET, in Centro Cardiologico Monzino – IRCCS of Milan between 2002 and 2020. Primary inclusion

criteria were previous or current evidence of HF symptoms [NYHA functional class I–III, stage C of the American College of Cardiologists/American Heart Association (ACC/AHA) classification], history of reduced LV systolic function (LVEF, ≤40%), stable clinical conditions with unchanged medications for at least 3 months, no major cardiovascular treatment or intervention scheduled, and capability to perform a maximal, symptom-limited CPET as confirmed by a peak respiratory exchange ratio (RER) ≥ 1.05. Conversely, the exclusion criteria were history of pulmonary embolism, primary valvular heart disease, pericardial disease, severe obstructive/restrictive lung disease, primary pulmonary hypertension, significant peripheral vascular disease, and exercise-induced angina and/or ST changes.

To assess the EOV prognostic impact, we firstly grouped those patients where the EOV presence has been identified by Corrà et al. criteria [16, 20] and compared them with a matched HFrEF population without EOV. Thereafter, we categorized the EOV group into two distinct subgroup according the EOV behavior during the exercise phase, i.e. disappearance versus persistence during the entire exercise.

The study was approved by local ethics committee, and all patients signed an informed consent form at the time of enrolment (CE n. R116/14-CCM127).

- Cardiopulmonary Exercise Test and EOV definition

A maximal, symptom-limited CPET was performed on an electronically braked cycloergometer connected to a metabolic chart (Vmax29C, SensorMedics; Cosmed Quark PFT, Cosmed SrL). A personalized ramp exercise protocol was chosen, aiming at a test duration of 10±2 minutes [21]. The exercise was preceded by a few minutes of resting breath-by-breath gas exchange monitoring and by a 3 min unloaded warm-up. A 12-lead electrocardiogram (ECG), blood pressure, and heart rate (HR) were also recorded. CPET was self-terminated by the subjects when they claimed that they had achieved maximal effort. However, we considered maximal or nearly maximal effort to be achieved if the respiratory exchange ratio (RER) was > 1.05 [22]. We performed a breath-by-breath analysis of expiratory gases and VE, and peak values were obtained in the last 20 seconds of exercise. The anaerobic threshold (AT) was identified through a V-slope analysis of VO_2 and carbon dioxide production (VCO_2), and it was confirmed through the specific behaviour of the ventilatory equivalents of O_2 (VE/VO_2) and CO_2 (VE/VCO_2) and through the end-tidal pressure of O_2 and CO_2 ($PetO_2$ and $PetCO_2$, respectively) . The end of the isocapnic buffering period was identified when

VE/VCO_2 increased and the end-tidal pressure of CO_2 decreased. The relationship between VE and VCO_2 was analysed as the slope (VE/VCO_2 slope) of the linear relationship between VE and VCO_2 from 1 minute after the beginning of loaded exercise to the end of the isocapnic buffering period [23,24].

For the study purpose, the presence of EOV was defined according the Corrà et al. criteria as VE cyclic fluctuations at rest persisting during effort at least for the 60% of the exercise duration, with an amplitude ≥ 15% of the average resting value [16,18, 20]. To be defined as truly positive for EOV, the amplitude of EOV must exceed 30% of concurrent mean VE with a complete oscillatory cycle within 40-140 seconds. Oscillations of similar frequency must also be visible in at least 3 of the other following variables: VO_2, VCO_2, RER, $PetO_2$ or $PetCO_2$. Furthermore, the HFrEF patients with EOV were further categorized into two subgroup according the EOV cessation at any time during the exercise phase (Group A, Figure 1, left pannels) or its persistence during the entire dynamic phase of the CPET (Group B) (Figure 1, right pannels). Eventually, starting from six variables [LVEF, hemoglobin (Hb), Modification of Diet in Renal Disease equation [MDRD], sodium levels (Na^+), pVO_2 and VE/VCO_2 slope), we also derived the MECKI score values from each patient according to the standard formula available online (https://www.cardiologicomonzino.it/en/meckiscore/) [6]. All tests were re-evaluated by experts blinded to patients' clinical features.

- Patients' Follow-Up and Study End-Point

Patients' follow-up was carried out according at Centro Cardiologico Monzino – IRCCS following the MECKI score research group suggestions and reported elsewhere [6]. In brief, follow-up started when clinical evaluation and CPET were performed, and it ended with the last clinical evaluation, or with the patient's death, cardiac transplantation or LV assistance device implantation (LVAD). The primary study study endpoint was a composite cardiovascular (CV) end-point including cardiovascular death plus heart transplantation or LVAD implantation. For completeness, a secondary end-point of total mortality was also explored.

- Statistical Analysis

Unless otherwise indicated, all data are expressed as the mean ± Standard Deviation (SD) whereas data with skewed distribution are given as median and interquartile range (75th percentile - 25th percentile). As a preliminary analysis, an extension of the Shapiro–Wilk test of normality was performed. Categorical variables were compared with a difference between proportion test; a two-sample t-test was used to compare the general characteristics and other continuous data between the study groups; Wilcoxon test was used to compare non-normally distributed variables.

We focused first on possible difference with respect the distribution of survival times at 5 years in the first two study groups (EOV Group and NoEOV Group) by adopting the Cox proportional hazards regression model. To determine whether a fitted Cox regression model adequately describes the data, we considered three kinds of diagnostics: (a) for violation of the assumption of proportional hazards, (b) for influential data, and (c) for nonlinearity in the relationship between the log-hazard and the predictors. A test of the proportional hazards assumption was performed for each covariate by correlating the corresponding set of scaled Schoenfeld residuals with a transformation of time based on the Kaplan-Meier estimate of the survival function. Focusing on residuals, a graphical diagnostic can be provided to check for influential observations. A matrix of estimated changes in the regression coefficients was obtained upon deleting each observation in turn. Then, the magnitudes of the largest obtained values were compared with the regression coefficients. Given that an incorrectly specified functional form in the parametric part of the model (eg, nonlinearity) might be a potential problem in Cox regression, the Martingale residuals were plotted against predictors to detect nonlinearity. Nonlinearity was obviously not an issue for dichotomous predictors.

As a confirmation of the first survival analysis, to exclude a possible interference of a number of general parameters known to impact *per se* on HF prognosis, we performed a 1:3 statistical matching (nearest neighbor matching) between the two study groups according to the main clinical variables possibly acting as confounders: age, gender, BMI, LVEF, Hb, Na^+, MDRD, and disease-modifying drugs prevalence (angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists/angiotensin receptor neprilysin inhibitor, beta-blockers, and mineralocorticoid receptor antagonists). A Kaplan-Meier analysis and a Cox regression model for the survival at 5 years were performed following the identical steps

previously described. These ensure that the EOV discriminates between deads and survivors on its own and as a further factor once VE/VCO_2 slope and pVO_2 effects are also taken into account.

Eventually, for the study purpose, we investigated possible difference with respect the distribution of survival times at 5 years within the lone EOV Group according to the EOV cessation (Group A) or persistence (Group B) during the dynamic phase of the exercise. Obviosly the two subgroups' distribution of survival times were also compared with the matched NoEOV population.

Statistical analysis was performed using R (R Develop-ment Core Team, 2009) packages. All tests were 2 sided. A P value less than or equal to 0.05 was considered as statistically significant.

RESULTS

Figure 2 shows schematically the step-by-step analyis starting from the initial HFrEF population and over the different study groups according to the EOV presence and its different behaviour.

Table 1 reports a detailed comparison between the main clinical, echocardiographic, laboratory, CPET data as well as concomitant therapeutic strategies collected at the study run-in in the overall HFrEF population (n 1.866 patients) and when categorized according to the EOV presence (NoEOV Group: 1,615 patients; EOV Group: 251 patients). The EOV group showed higher age and prevalence of male gender, lower LVEF, as well as a more severe functional impairment both in terms of NYHA classification and CPET-derived data (i.e. pVO_2 and VE/VCO_2 slope), whereas no significant differences were found between groups with respect to the main laboratory data and ischaemic etiology. The median MECKI score value in the EOV Group was three times higher than in the noEOV Group ($p < 0.001$). Eventually, within the disease-modifying drugs' categories, there was a similar representation of treatment with angiotensin converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitor; (ACE-i/ARBs/ARNi) or β-blockers but a higher prevalence of mineralocorticoid receptor antagonists (MRA) treatment in the EOV Group than in the couterpart.

The median follow-up was 1.406 days (25^{th}–75^{th} interquartile range, 564-2.901 days). Survival analysis showed a significantly better CV outcome of the NoEOV Group compared to the counterpart (Figure 3, panel A), being the prespecified CV end-point occurred in 211 NoEOV patients (13.1%) and 68

(27.1%) EOV patients (p<0.001) with most of the events registered within the fifth years of follow up [140 patients (8.7% event rate) in the NoEOV Group and 57 patients (22.7% event rate) in the EOV Group].

After the 3:1 matching according to age, gender, NYHA class, Hb, Na^+, MDRD and disease modifier drugs, 741 NoEOV patients were matched with 247 EOV patients. Interestingly, the survival matched analysis confirmed the just observed unfavorable outcome of those HFrEF patients with EOV with respect the counterpart (Figure 3, panel B). Even when VE/VCO_2 slope and pVO_2 were added as predictors, the EOV Group showed a significantly poorer CV outcome than noEOV Group ($p < 0.05$). As expected, both other CPET-derived variables, i.e. the VE/VCO_2 slope and pVO_2, were independently associated to the primary CV end-point ($p < 0.001$).

Table 2 reports a detailed comparison within EOV Group when categorized according to the EOV cessation (Group A: 142 patients) or its persistence during the entire dynamic phase of the CPET (Group B: 109 patients). Albeit almost overlapping with respect clinical and laboratory as well as therapeutic strategies at the study run-in, patients owing to the Group A showed a significantly better functional status in terms of NYHA classification and CPET-derived data. Also, the median MECKI score value in Group B was slighly higher than in Group A ($p = 0.037$). However, the survival analysis at 5 years did not found any significant difference between these two EOV subgroups being the prespecified CV end-point at the fifth year occurred in 33 Group A patients (23.2%) and 25 (22.9%) Group B patients ($p = 0.15$) (Figure 3, panel C).

With respect the secondary prespecified end-point, i.e., total mortality, the survival analysis did not achieve any significance, the EOV group suffering from a similar outcome than the noEOV Group even at the matched analysis. Indeed, at the fifth year, 166 NoEOV patients (22.4%) and 77 (30.1%) EOV patients died (p=Ns). Again, also the analysis within the EOV group according the EOV behaviuor, did not find significant difference in total mortalty between Group A and Group B [at 5-years, 45 Group A patients (32.1%) and 32 (29.9%) Group B patients died (p=Ns).

DISCUSSION

The main findings of the present single-center retrospective analysis, carried out on a sizeable cohort of nearly two thousands HFrEF patients, might be summarized as follows: a) in our setting of stable HFrEF patients on optimized drugs regimen, the EOV prevalence stands around 13%; b) HFrEF patients with

EOV suffers from a worse clinical and functional status than the counterpart, thus arguing in favor of the EOV appearance in a most advanced HF stage; c) EOV presence represents an undoubted negative prognostic marker in terms of cardiovascular events risk but not of total mortality, this effect remaining significant even after accounting for the main clinical variables possibly acting as confounders; d) although the group of patients with EOV persistence during all the exercise time showed a more severe functional impairment than those with EOV early cessation, the event-free survival rate at 5 years did not differ significantly.

In the last decades, growing attention has been given to the analysis of the ventilatory responses to exercise in the HFrEF setting [2,3,25], the VE being a fascinating crossroad between the lung function, the hemodynamic equilibrium and the autonomic nervous system activity [26]. Indeed, although the VE control is regulated primarily by the alveolar-capillary unit [2,25,27,28], carotid chemoceptors and medulla interactions [1,29,30], it is also dependent from the circulation time responsible of the "information transfer" (O_2 and CO_2) [31,32] as well as from the neurohormonal milieu able to impact directly on the chemoceptors sensitivity and, eventually, from the baroreflex activity [33-35]. Thus, starting from the physiology [1,29], most of the VE abnormalities observed in the HFrEF can be interpreted and, then, used to understand its pathophysiology [2,5], to improve its risk stratification [3,4,6,9-14] and, possibly, to direct the physician towards specific therapeutic options [35,36-39]. In such a context, EOV might represent a reliable marker of an advanced disease stage characterized from a full derangement of the VE control chain due to a further circulation delay, a chemoceptors hypersensitivity as well as baroreflex impairment [9,16,18]. The present study argues in favor of the abovementioned concept since it demonstrates older age, lower LVEF values as well as a worse functional status (i.e. NYHA, pVO_2 and VE/VCO_2 slope) in the HFrEF Group with EOV than in the counterpart. In addition, as expected, EOV Group showed a median MECKI score value more than three times higher than the noEOV Group (12.1% versus 3.9%), thus identifying this category as a particularly high-risk HFrEF setting [6-8]. Furthermore, our survival analysis shows a higher rate of hard cardiovascular events (death, need for urgent heart transplant or LVAD implantation) in the HFrEF Group with EOV even after a close matching accounting for possible confounders, thus reinforcing the need to include the EOV into the CPET-derived list of markers able to

identify those HFrEF patients at the highest cardiovascular events risk [17]. Of note, the present was one of the largest studies specifically focusing on the EOV in a homogeneous cohort of stable HFrEF patients on optimized treatment and it fixes its prevalence at around 13%, a datum slightly blunted with respect the literature reporting average values of 15-20% (ranging from 7 to 30%) [15-18]. In addition to all the possible differences in the studies characteristics (i.e. sample size, HF category explored, concomitant therapies, etc), another possible cause for this discrepancy might be that, in the present study, the criterion adopted to define the EOV was those of Corrà and colleagues (i.e. resting VE cyclic fluctuations persisting during effort at least for the 60% of the exercise duration, with an amplitude ≥ 15% of the average resting value) [16,40] and that all doubtful cases were excluded.

Besides reinforcing the need to include the EOV into a CPET-centered evaluation of the HFrEF patients, the present study sought also to explore in detail the possible EOV clinical and prognostic meaning with respect to its disappearance/persistence during the exercise. Little information is available as regards the causes of EOV disappearance during exercise and we know from the study of Schmidt et al. that EOV is associated with an increase cost of breathing and its disappearance during exercise allows a step up of the VO_2/work relationship slope [41]. JP Schmidt observation is in line with the present finding of a worst exercise performance impairment in HF patients with EOV persistence versus EOV disappearance during exercise. However, the real clinical implications of these two distinct EOV behaviors have been investigated only in a recent interesting study by da Luz Goulart and colleagues, where the HFrEF patients with EOV persistence showed the worst clinical profile as well as the poorest cardiovascular outcome [19]. However, we did not confirm the observation of a possible association between the EOV persistence and prognosis, being a number the possible underlying reasons for these conflicting results. Albeit both single-center, the two studies are significantly different with respect the sample size (1.866 versus 315 patients enrolled) as well as the follow-up length which was more than double in the present study. Furthermore, rather than an all-cause death end-point such as the one explored by da Luz Goulart, we explored a pure cardiovascular end-point (i.e. cardiovascular death, need for urgent heart transplant or LVAD implantation). Of note, some differences in the general (i.e. age, BMI) and clinical (i.e. LVEF values, comorbidities and follow up modalities) characteristics of the samples analyzed cannot be excluded. Eventually, although Group B

showed a median MECKI score value slightly higher than Group A, it is also conceivable that in a such small and high-risk setting, even the MECKI score might have encountered some problems in further refining the true risk profile. Indeed, the patients' recruitment was almost 20 years long, between 2002 and 2020, a period of time during which HF treatment and follow up modalities improved significantly and we did not take into account this variable. Indeed, we have previously shown that for a given MECKI score or MECKI score variables the real prognosis was also related to recruitment time [42].

LIMITATIONS

A few limitations should be acknowledged, the first one being the single-center retrospective nature of the study. However, it should be noted that present data came from a sizable HFrEF cohort with a long follow-up as well as that the center involved was highly experienced with the HF management and CPET analysis. Secondly, we are aware that the present study examined the EOV prognostic impact at a single time point and, accordingly, considering the long follow-up period, we cannot exclude that changes in some clinical strategies altered our survival analysis as well as a possible patients' transition to another group category [42,43].

Moreover, mainly due to technical reasons, in such a large retrospective cohort with a follow-up starting in some cases more than 20 years ago, we were not able to supply data and to speculate about the EOV cycle length and amplitude, both parameters recently showed as significantly correlated with brain natriuretic peptide levels [20]. In such a context, thanks to the development of dedicated software for the EOV analysis, it is likely that these specific EOV feature will be easily and reliably available for physicians in the next future and we firmly believe that this advance will represent a further step ahead into HF clinical management [44].

Last, our survival analysis accounted for hard events only such as cardiac death and need for urgent heart transplantation or LVAD implantation (primary CV end-point) and total mortality (secondary end-point), this approach preventing us from any speculation on possible specific attitude of the EOV and/or its behavior in identifying the HF hospitalization risk or, even, the cause of death (i.e. sudden cardiac death, worsening HF, etc).

CONCLUSIONS

Present analysis, albeit retrospective, strongly encourage that the EOV *per se* should be taken into account as part of the HFrEF clinical and prognostic assessment, provided its identification by certain criteria. Indeed, we confirmed that the EOV presence is associated with a more advanced HFrEF stage in terms of both clinical and functional status as well as with an unfavorable cardiovascular outcome. However, at the present analysis, the EOV behavior, in terms of early cessation or persistence, does not emerge as a further prognostic marker in HFrEF patients. Other studies are needed to further investigate the EOV underlying mechanisms and its characteristics (i.e. amplitude, cycle length and duration) in order to maximize its clinical and prognostic value.

SOURCES OF FUNDING:

This study was supported by Italian Ministry of health.

DISCLOSURES

Nothing to disclose.

Authors statement

DM, ES, PP and PA contributed to the conception of the work; DM, AM and PADL contributed to data analysis; DM, EF, PG, GG, PP, CV, IM, SS, AM contributed to data interpretation; DM, GG and EF drafted the manuscript; PA, ES and MM critically revised the manuscript. All the Authors contributed to data collection and finally approved the version to be published.

REFERENCES

1. Wasserman K. Breathing during exercise. N Engl J Med 1978;298(14):780-5.
2. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. Circulation. 1997;96(7):2221-7.

3. Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol. 1997;29(7):1585-90.
4. Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation. 2002;106(24):3079-84.
5. Agostoni P, Sciomer S, Palermo P, et al. Minute ventilation/carbon dioxide production in chronic heart failure. Eur Respir Rev. 2021;30(159):200141.
6. Agostoni P, Corrà U, Cattadori G, et al; MECKI Score Research Group. 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(6):2710-8.
7. Corrà U, Agostoni P, Giordano A, et al; MECKI Score Research Group. The metabolic exercise test data combined with Cardiac And Kidney Indexes (MECKI) score and prognosis in heart failure. A validation study. Int J Cardiol. 2016;203:1067-72.
8. Agostoni P, Paolillo S, Mapelli M, et al. Multiparametric prognostic scores in chronic heart failure with reduced ejection fraction: a long-term comparison. Eur J Heart Fail. 2018;20(4):700-10.
9. Ponikowski P, Anker SD, Chua TP, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. Circulation 1999;100:2418–24.
10. Leite JJ, Mansur AJ, de Freitas HF, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. J Am Coll Cardiol. 2003 Jun 18;41(12):2175-81.
11. Guazzi M, Raimondo R, Vicenzi M, et al. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. J Am Coll Cardiol. 2007;24;50(4):299-308.
12. Sun XG, Hansen JE, Beshai JF, et alOscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol. 2010;55(17):1814-23.
13. Rovai S, Corrà U, Piepoli M, et al.; MECKI Score Research Group. Exercise oscillatory ventilation and prognosis in heart failure patients with reduced and mid-range ejection fraction. Eur J Heart Fail. 2019;21(12):1586-95.

14. Cornelis J, Beckers P, Vanroy C, et al. An overview of the applied definitions and diagnostic methods to assess exercise oscillatory ventilation--a systematic review. Int J Cardiol. 2015;190:161-9.
15. Agostoni P, Corrà U, Emdin M. Periodic Breathing during Incremental Exercise. Ann Am Thorac Soc. 2017;14:S116-S122
16. Corrà U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. Chest. 2002;121(5):1572-80.
17. Balady GJ, Arena R, Sietsema K, et al.; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191-225.
18. Corrà U. Exercise oscillatory ventilation in heart failure. Int J Cardiol 2016;206:S13-S15.
19. da Luz Goulart C, Agostoni P, Salvioni E, et al. Exercise oscillatory breathing in heart failure with reduced ejection fraction: clinical implication. Eur J Prev Cardiol. 2022 Sep 7;29(12):1692-8.
20. Ribeiro GDS, Deresz LF, Salvioni E, Hansen D, Agostoni P, Karsten M. Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients. Int J Cardiol. 2022;360:39-43.
21. Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. Int J Cardiol. 2019;288:107-13
22. Piepoli MF, Corrà U, Agostoni PG, et al. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendation for performance and interpretation. I. Definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2006;13:150-64.
23. Magrì D, Agostoni P, Corrà U, et al. Deceptive meaning of oxygen uptake measured at the anaerobic threshold in patients with systolic heart failure and atrial fibrillation. Eur J Prev Cardiol. 2015;22:1046-55.

24. Wasserman K, Hansen JE, Sue DY, et al. Clinical Exercise Testing. Principles of Exercise Testing and Interpretation Including Pathophysiology and Clinical Applications. Lippincott Williams & Wilkins: Philadelphia 2005;138-139
25. Apostolo A, Giusti G, Gargiulo P, et al. Lungs in heart failure. Pulm Med. 2012;2012:952741.
26. Gentile F, Fabiani I, Emdin M. Exercise oscillatory ventilation in heart failure and brain-lung-heart-muscle crosstalk. Eur J Prev Cardiol. 2022;29(12):1689-91.
27. Agostoni PG, Bussotti M, Palermo P, et al. Does lung diffusion impairment affect exercise capacity in patients with heart failure? Heart. 2002;88(5):453-9.
28. Magrì D, Brioschi M, Banfi C, et al. Circulating plasma surfactant protein type B as biological marker of alveolar-capillary barrier damage in chronic heart failure. Circ Heart Fail. 2009;2(3):175-80.
29. Dowell AR, Buckley CE 3rd, Cohen R, et al. Cheyne-Stokes respiration. A review of clinical manifestations and critique of physiological mechanisms. Arch Intern Med. 1971;127(4):712-26.
30. Ponikowski P, Chua TP, Anker SD, et al. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. Circulation. 2001;104(5):544-9.
31. Murphy RM, Shah RV, Malhotra R, et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. Circulation. 2011;124(13):1442-51.
32. Giannoni A, Raglianti V, Taddei C, et al. Cheyne-stokes respiration related oscillations in cardiopulmonary hemodynamics in patients with heart failure. Int J Cardiol 2019;289:76-82.
33. Giannoni A, Gentile F, Navari A, et al. Contribution of the lung to the genesis of cheyne-stokes respiration in heart failure: plant gain beyond chemoreflex gain and circulation time. J Am Heart Assoc 2019;8:e012419.
34. Aimo A, Saccaro LF, Borrelli C, et al. The ergoreflex: how the skeletal muscle modulates ventilation and cardiovascular function in health and disease. Eur J Heart Fail. 2021;23:1458-67.
35. Ribeiro GS, Cargnin C, Dal Lago P, et al. Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis. Eur J Prev Cardiol. 2022;29:e233-6

36. Gong J, Castro RRT, Caron JP, et al. Usefulness of ventilatory inefficiency in predicting prognosis across the heart failure spectrum. ESC Heart Fail. 2022;9(1):293-302.
37. Agostoni P, Cattadori G, Bussotti M, et al. Cardiopulmonary interaction in heart failure. Pulm Pharmacol Ther. 2007;20(2):130-4.
38. Sinagra G, Corrà U, Contini M, et al. Choosing among β-blockers in heart failure patients according to β-receptors' location and functions in the cardiopulmonary system. Pharmacol Res. 2020;156:104785.
39. Cundrle I Jr, Johnson BD, Rea RF, et al. Mitigation of Exercise Oscillatory Ventilation Score by Cardiac Resynchronization Therapy. J Card Fail. 2020;26(10):852-40.
40. Ribeiro GDS, Deresz LF, Salvioni E, et al. Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients. Int J Cardiol. 2022;360:39-43.
41. Schmid JP, Apostolo A, Antonioli L, et al. Influence of exertional oscillatory ventilation on exercise performance in heart failure. Eur J Prev Cardiol. 2008;15:688-92.
42. Paolillo S, Veglia F, Salvioni E, et al. Heart failure prognosis over time: how the prognostic role of oxygen consumption and ventilatory efficiency during exercise has changed in the last 20 years. Eur J Heart Fail. 2019;21(2):208-17.
43. Pezzuto B, Piepoli M, Galotta A, et al. The importance of re-evaluating the risk score in heart failure patients: An analysis from the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score database. Int J Cardiol. 2023;376:90-96.
44. Dos Santos Ribeiro G, Beltrame T, Fernando Deresz L, et al. Software development to standardize the clinical diagnosis of exercise oscillatory ventilation in heart failure. J Clin Monit Comput. 2023 Feb 3. doi: 10.1007/s10877-023-00976-9.

FIGURE LEGENDS

Figure 1. Exertional Oscillatory Ventilation behaviors.

Representative examples of the two distinct exercise oscillatory ventilation temporal behaviors during cardiopulmonary exercise test. **Left panel**: EOV cessation during the exercise phase; **Right Panel**: EOV persistence during the whole dynamic phase. VE: ventilation; RQ: respiratory quotient; $PetO_2$: pressure end-tidal of oxygen; $PetCO_2$: pressure end-tidal of carbon dioxide. t: time in minutes. Note that the Corrà et al. criteria has been adopted for EOV definition, i.s. resting VE cyclic fluctuations persisting during effort at least for the 60% of the exercise duration, with an amplitude ≥ 15% of the average resting value [15].

Figure 2. Step-by-step study phases.

Diagram showing the step-by-step analyis starting from the initial heart failure and reduced ejection fraction (HFrEF) population and over the various study groups according to the exertional oscillatory ventilation (EOV) presence and its different behavior. Pts: patients; LvEF: left ventricular ejection fraction; NYHA: New York Heart Association; BMI: body mass index; Hb: haemoglobin; Na: sodium levels; MDRD: Modification of Diet in Renal Disease equation.

Figure 3. Survival analysis according to exertional oscillatory ventilation (EOV) and its behaviors.

Kaplan-Meier estimator (KM) of the primary cardiovascular endpoint at 5 years [cardiovascular mortality, heart transplant, left ventricular assistance device implantation]. **Upper panels:** KM according to EOV presence in the entire heart failure with reduced left ventricular ejection fraction (HFrEF) cohort. **Middle Panels:** KM according to EOV presence conditional on the main clinical variables possibly acting as confounders (i.e. matched analysis see Methods section for details); **Lower Panels:** KM according EOV behavior (i.e. EOV cessation, Group A versus EOV persistence, Group B).

TABLE 1. Main clinical variables of the overall HFrEF population and according to the presence of an exertional oscillatory ventilation (EOV) during the exercise

General data	**Overall HFrEF (n. 1.866)**	**NoEOV Group (n. 1.615)**	**EOV Group (n. 251)**
Age, years	65±11	64±11	67±10†
Male, n %	1,510 (81)	1,288 (80)	222 (88) †

BMI, kg/m^2	26.5±4.2	26.6±4.2	25.8±4.1†
NYHA, n (%)			
I	278 (15)	258 (16)	20 (8)*
II	975 (52)	875 (54)	100 (40) †
III	613 (33)	482 (30)	131 (52)*
Ischemic etiology, n (%)	928 (50)	812 (50)	116 (46)
LVEF, %	30 ± 8	32 ± 7	28 ± 8*
Sodium, mmol/L	139 ± 3	139 ± 3	139 ± 3
Haemoglobin, g/dL	13.7 ± 1.7	13.7 ± 1.7	13.7 ± 1.8
MDRD, ml/min*1.73m^2	72.4 ± 21.6	74.2 ± 23.6	61.2 ± 22.3†
MECKI score, %	4.1 [8.6]	3.9 [7.5]	12.1 [19]
CPET variables			
Peak VO_2, ml/kg/min	14.9 ± 4.6	15.3 ± 4.6	12.4 ± 3.4*
Peak VO_2, % of predicted	58 ± 17	59 ± 16	49 ± 16*
VE/VCO_2 slope	32.8 ± 8.2	32.9 ± 7.6	38.4 ± 9.7*
Treatment			
ACEi, ARBs or ARNi, n (%)	1.608 (86)	1.395 (86)	213 (85)
β-blockers, n (%)	1.627 (87)	1.401 (87)	226 (91)
MRA, n (%)	1.089 (58)	915 (56)	174 (69)*

Data are expressed as mean±SD, as absolute number (% on total sample) or as median [75th-25th percentile]. *p<0.001; †p<0.01. BMI: body mass index; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; MDRD: Modification of Diet in Renal Disease equation; MECKI: Metabolic Exercise combined with Cardiac and Kidney Indexes; VO_2: oxygen uptake; VE/VCO_2 slope: ventilation versus carbon dioxide production relationship; ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; ARNi: angiotensin receptor neprilysin inhibitor; MRA: mineralocorticoid receptor antagonists.

TABLE 2. Main clinical variables of the EOV Group categorized according to the early cessation (Group A) or its persistence during the entire dynamic phase of the CPET (Group B)

General data	**Group A (n. 142)**	**Group B (n. 109)**

Age, years	67±10	68±10
Male, n %	122 (85)	100 (91)
BMI, kg/m^2	26.1±3.9	25.5±4.2
NYHA, n (%)		
I	13 (9)	7 (6)
II	63 (44)	37 (34)§
III	62 (44)*	69 (63)*
Ischemic etiology, n (%)	69 (49)	47 (43)
LVEF, %	28 ± 8	29 ± 8
Sodium, mmol/L	138 ± 3	139 ± 4
Haemoglobin, g/dL	13.7 ± 1.6	13.8 ± 1.9
MDRD, ml/min*1.73/m^2	61.2 ± 22.3	63.2 ± 26.2
MECKI score, %	10.9 [16]	13.1 [24] ‡
CPET variables		
Peak VO_2, ml/kg/min	13.2 ± 3.3	11.2 ± 3.1
Peak VO_2, % of predicted	53 ± 15	44 ± 16*
VE/VCO_2 slope	37.2 ± 8.7	39.5 ± 10.7*
Treatment		
ACEi, ARBs or ARNi, n (%)	120 (84)	93 (85)
β-blockers, n (%)	127 (89)	99 (92)
MRA, n (%)	94 (66)	80 (73)

See table 1 for other abbreviations. *p < 0.001; †p < 0.01; ‡ p < 0.05

HIGHLIGHTS

- EOV prevalence stands at 10-15% in a HFrEF population on optimized treatment
- EOV characterizes *per se* a more advanced HFrEF stage with an unfavorable CV outcome
- EOV identification should be part of the core CPET-variables in HFrEF assessment
- EOV persistence during the entire CPET does not emerge as a reliable prognostic marker

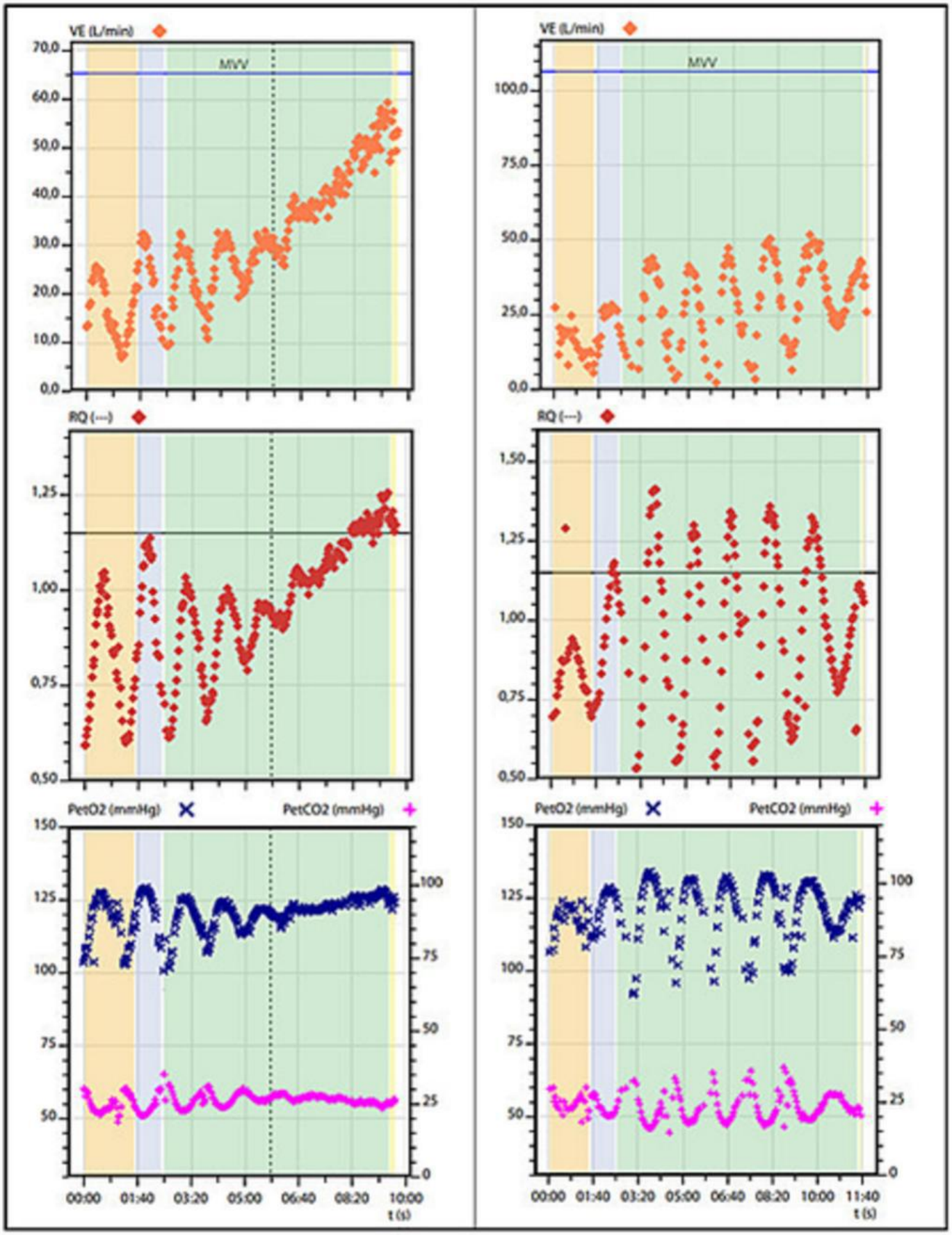

Figure 1

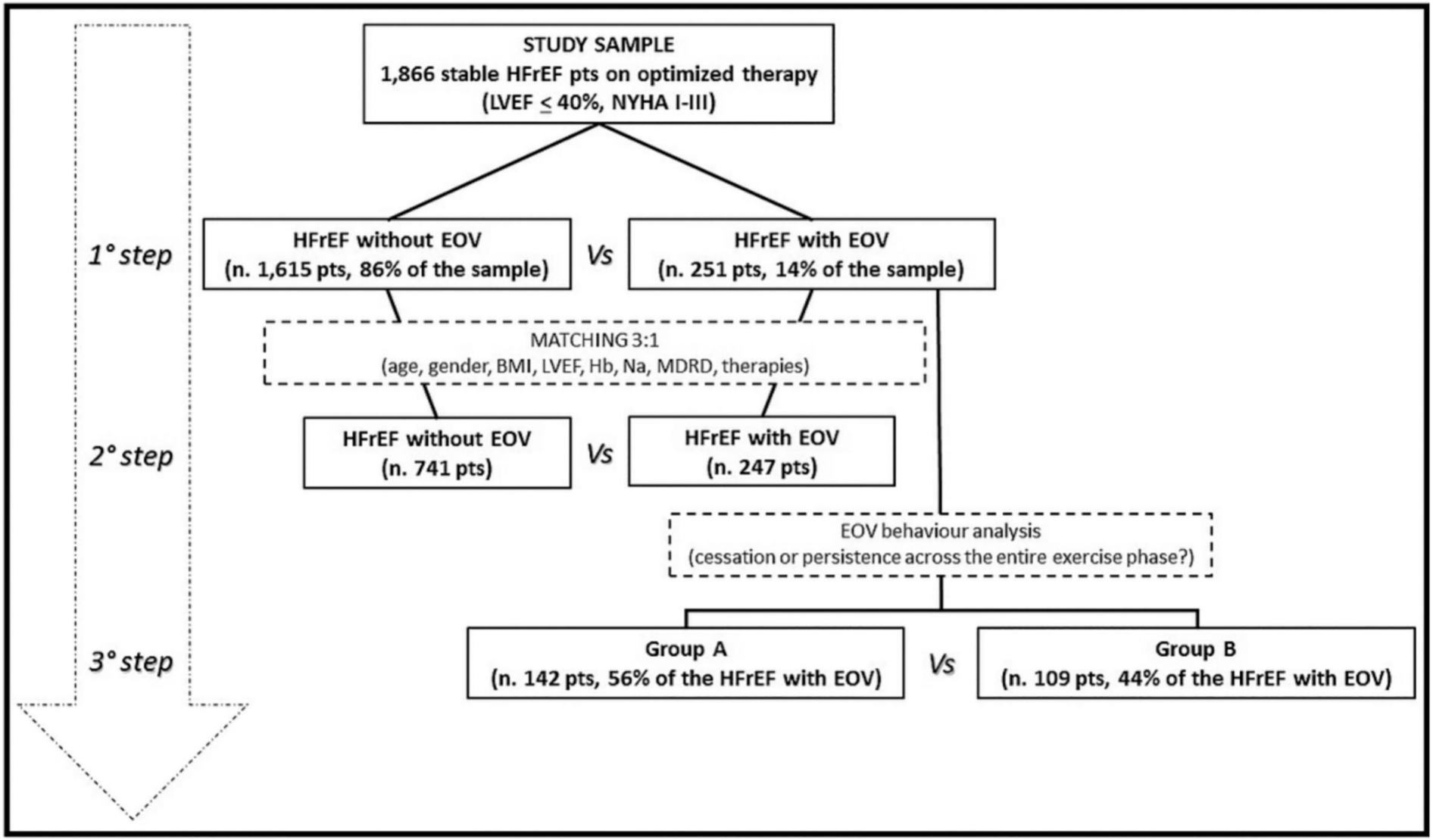
STUDY SAMPLE
1,866 stable HFrEF pts on optimized therapy
(LVEF ≤ 40%, NYHA I-III)
1° step
HFrEF without EOV
(n. 1,615 pts, 86% of the sample)
Vs
HFrEF with EOV
(n. 251 pts, 14% of the sample)
MATCHING 3:1
(age, gender, BMI, LVEF, Hb, Na, MDRD, therapies)
2° step
HFrEF without EOV
(n. 741 pts)
Vs
HFrEF with EOV
(n. 247 pts)
EOV behaviour analysis
(cessation or persistence across the entire exercise phase?)
3° step
Group A
(n. 142 pts, 56% of the HFrEF with EOV)
Vs
Group B
(n. 109 pts, 44% of the HFrEF with EOV)

Figure 2

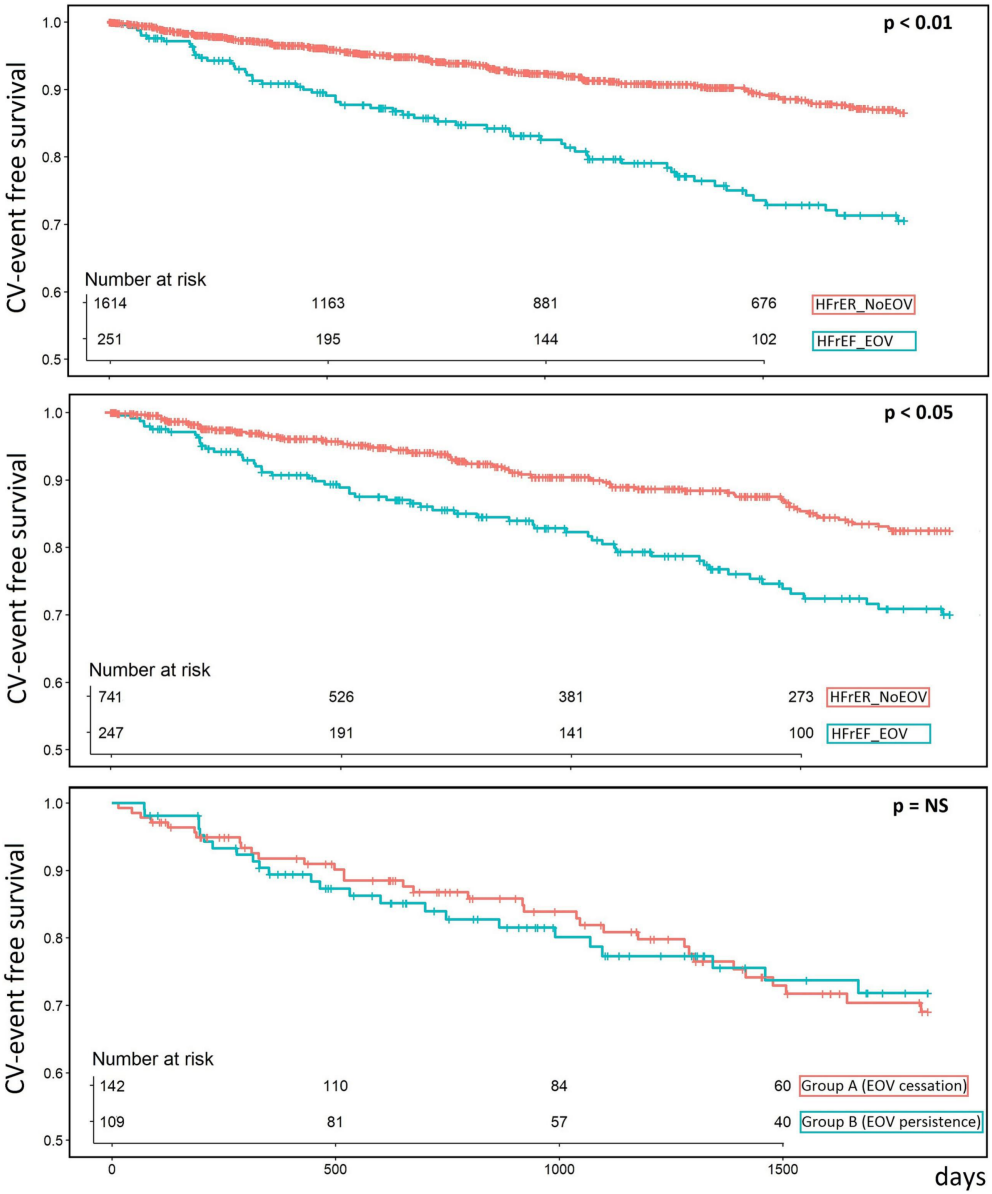
p < 0.01
CV-event free survival
1.0
0.9
0.8
0.7
0.6
0.5
Number at risk
1614
1163
881
676
HFrER_NoEOV
251
195
144
102
HFrEF_EOV
p < 0.05
CV-event free survival
Number at risk
741
526
381
273
HFrER_NoEOV
247
191
141
100
HFrEF_EOV
p = NS
CV-event free survival
Number at risk
142
110
84
60
Group A (EOV cessation)
109
81
57
40
Group B (EOV persistence)
0
500
1000
1500
days

Figure 3