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Exercise training reverses exertional oscillatory ventilation in heart failure patients

Marzena Zurek*, Ugo Corrà#, Massimo F. Piepoli¶, Ronald K. Binder*, Hugo Saner* and Jean-Paul Schmid*

ABSTRACT: Exertional oscillatory ventilation (EOV) is an ominous prognostic sign in chronic heart failure (CHF), but little is known about the success of specific therapeutic interventions.

Our aim was to study the impact of an exercise training on exercise capacity and cardiopulmonary adaptation in stable CHF patients with left ventricular systolic dysfunction and EOV.

96 stable CHF patients with EOV were included in a retrospective analysis (52 training *versus* 44 controls). EOV was defined as follows: 1) three or more oscillatory fluctuations in minute ventilation (V'_E) during exercise; 2) regular oscillations; and 3) minimal average ventilation amplitude $\geqslant$5 L.

EOV disappeared in 37 (71.2%) out of 52 patients after training, but only in one (2.3%) out of 44 without training ($p<0.001$). The decrease of EOV amplitude correlated with changes in end-tidal carbon dioxide tension ($r= -0.60$, $p<0.001$) at the respiratory compensation point and V'_E/V'_{CO_2} slope ($r=0.50$, $p<0.001$). Training significantly improved resting values of respiratory frequency (f_R), V'_E, tidal volume (V_T) and V'_E/V'_{CO_2} ratio. During exercise, V'_E and V_T reached significantly higher values at the peak, while f_R and V'_E/V'_{CO_2} ratio were significantly lower at submaximal exercise. No change was noted in the control group.

Exercise training leads to a significant decrease of EOV and improves ventilatory efficiency in patients with stable CHF.

KEYWORDS: Cardiopulmonary exercise test, congestive heart failure, exercise training, oscillatory ventilation, periodic breathing, rehabilitation

Cardiopulmonary exercise testing (CPET) parameters are strong indicators of disease severity and prognosis in chronic heart failure (CHF) patients: peak oxygen uptake (V'_{O_2}) [1] and ventilatory efficiency (minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope) are traditionally considered the strongest predictors [2], but exertional oscillatory ventilation (EOV) has recently emerged as a new index linked with poor prognosis [3–5].

EOV consists of cyclic hyper- and hypopnoea, characterised by an oscillatory kinetic in V'_{O_2} and V'_{CO_2}, with a period that varies from 45 to 90 s. It has been reported to occur in 12–30% of CHF patients during CPET [3, 4], depending on the severity of the disease. Until now, reports on patients with EOV have focussed mainly on the description of their clinical characteristics, behaviour during CPET and prognostic value, but little is known about the impact of specific therapeutic interventions to reverse EOV. Nevertheless, an improvement in the central haemodynamic status by milrinone or heart transplantation [6], as well as aerobic training combined with inspiratory muscle training [7], seems to affect ventilatory oscillations.

Two hypotheses have been postulated on the genesis of EOV. The ventilatory hypothesis assumes an instability of breathing control due to abnormal chemoreceptor feedback [8–10], whereas reduced cardiac output or cardiac output fluctuations constitute the haemodynamic hypothesis of EOV occurrence [11–14].

Aerobic endurance training in CHF patients improves ventilatory efficiency, central haemodynamic factors and peripheral muscle chemoreflex response, which are all implicated in the genesis of EOV. We hypothesised that an aerobic

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AFFILIATIONS
*Cardiovascular Prevention and Rehabilitation, Dept of Cardiology, Bern University Hospital, and University of Bern, Bern, Switzerland.
#Division of Cardiology, Salvatore Maugeri Foundation, IRCCS, Veruno, and
¶Heart Failure Unit, Cardiology Dept, Guglielmo da Saliceto Polichirurgico Hospital, Piacenza, Italy.

CORRESPONDENCE
J-P. Schmid
Cardiovascular Prevention and Rehabilitation, Swiss Cardiovascular Centre Bern
University Hospital (Inselspital)
3010 Bern
Switzerland
E-mail: jean-paul.schmid@insel.ch

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exercise training programme could result in an improvement of EOV due to its potential counteracting effects of exercise on the main causative factors of EOV.

METHODS

We studied the impact of a short-term exercise training programme on ventilatory and haemodynamic parameters in 96 stable CHF patients with EOV, of whom 52 patients were undergoing a 3-month outpatient exercise training programme and 44 patients served as a control. Our study is a retrospective analysis of data derived from the outpatient cardiac rehabilitation clinic at the University Hospital Bern, Bern, Switzerland (exercise training (n=52) and controls (n=8)) and exercise laboratories in Veruno (n=25) and Piacenza (n=11), Italy (controls only).

All patients had a left ventricular ejection fraction <40% and were in a stable clinical condition. An incremental symptom limited CPET on a cycle ergometer was performed at baseline and after 3 months of training or control phase. Patients with angina or signs of myocardial ischaemia, relevant obstructive lung disease (Tiffeneau ratio <70% and forced expiratory volume in 1 s <60% predicted) or reduced vital capacity (<60% pred), congenital heart disease with the presence of a shunt or any orthopaedic condition that could have limited the subject's ability to profit from exercise training were excluded from the study.

Exercise training programme

The exercise training programme was attended three times a week for a period of 3 months. The programme included 36 exercise and 12 information sessions. Each training session consisted of two units of 45 min, composed mainly of aerobic endurance training performed on a cycle ergometer and in the form of calisthenic exercises. Training intensity was set between 60 and 80% of peak V'_{O_2}, determined by a preliminary CPET.

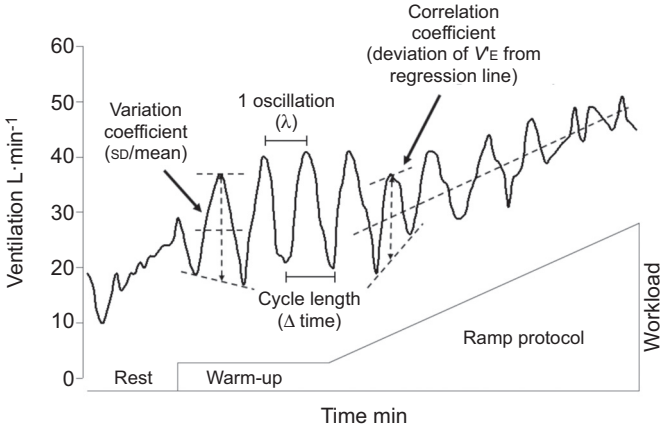

FIGURE 1. Example of a patient presenting with exercise oscillatory ventilation (EOV). For the definition of EOV, the following criteria had to be fulfilled: 1) at least three regular oscillations; 2) regular oscillation, defined as a standard deviation of three consecutive cycle lengths (time between two consecutive nadirs) within 20% of the average; 3) a minimal average amplitude of ⩾5 L (peak value minus the average of two adjacent nadirs). The magnitude of EOV during warm-up was measured by the variation coefficient of minute ventilation (V'_E). To account for the change in increase of V'_E due to increasing workload, EOV magnitude during incremental exercise was measured by the correlation coefficient of V'_E. Δ: change; λ: wavelength.

Clinical assessment and data analysis

At baseline and after 3 months, all patients underwent echocardiographic evaluation (Sequoia C512; Siemens Medical Solutions, Mountain View, CA, USA, and GE Vivid 7; GE Medical Systems, Waukesha, WI, USA) and CPET. Before exercise testing, spirometry was performed in all patients, followed by a symptom-limited CPET using an upright, computer-controlled, rotational speed independent cycle ergometer. For spirometry and CPET (breath-by-breath measures), an Oxycon Alpha® (Jaeger-Toennies, Höchberg, Germany) was used in the laboratory in Bern, and a Vmax 29C (SensorMedics USA, Homestead, FL, USA) in the laboratories in Veruno and Piacenza. Acquisition of resting data was followed by an unloaded cycling warm-up period of up to 3 min. Thereafter, a personalised ramp protocol was used for each patient, with the objective of reaching maximum exercise capacity within 8–12 min.

Values of V'_E, respiratory frequency (f_R) and tidal volume (V_T) at rest and during warm-up are reported as averages obtained over 60 s (the last 60 s during warm-up), whereas the values at the respiratory compensation point (RCP) and at peak exercise were averaged over 30 s. Resting end-tidal carbon dioxide tension (P_{ET,CO_2}) was collected for 60 s prior to exercise in the seated position, whereas the value at the RCP was averaged over 30 s. Peak V'_{O_2} was computed as the 60-s average values of V'_{O_2} during the last stage of the exercise test. The slope of V'_E *versus* V'_{CO_2} was calculated as a linear regression function, excluding the nonlinear part of the relationship after the RCP. All subjects had to reach a respiratory exchange ratio (RER) ⩾1.05.

The RCP was defined using the following criteria: 1) the point after which a nonlinear rise in V'_E occurred relative to V'_{CO_2}; and 2) the continuous decrease of P_{ET,CO_2} following its peak.

TABLE 1 Patient characteristics

	EOV training	EOV control	p-value
Subjects n	52	44	
Age yrs	58±10	59±13	0.413
Males/females n	47/5	39/5	0.780
BMI kg·m^{-2}	26.1±4.6	25.9±4.4	0.961
Aetiology ischaemic/ nonischaemic n	22/30	27/17	0.063
Atrial fibrillation n	13 (25)	5 (12)	0.090
LVEF %	27.3±8.9	26.7±8.8	0.767
LVEDD mm	67.4±10.1	65.8±9.1	0.350
Medication at baseline			
ACE inhibitors or ARBs	52 (100)	42 (96)	0.120
β-blockers	47 (90)	33 (75)	0.056
Diuretics	42 (81)	36 (82)	0.779
Medication at follow-up			
ACE inhibitors or ARBs	52 (100)	42 (96)	0.120
β-blockers	48 (92)	34 (77)	0.046
Diuretics	43 (83)	36 (82)	0.424

Data are presented as mean±SD or n (%), unless otherwise stated. EOV: exertional oscillatory ventilation; BMI: body mass index; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers.

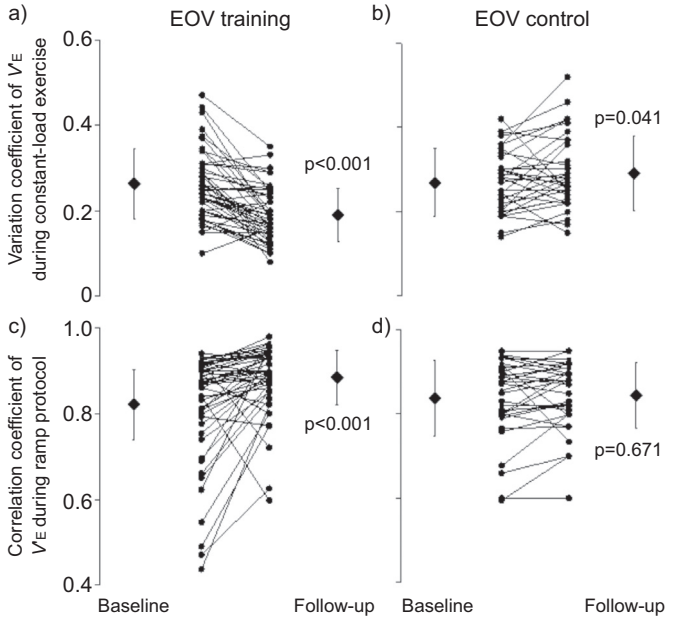

FIGURE 2. a, b) Variation coefficient and c, d) correlation coefficient in the exertional oscillatory ventilation (EOV) a, c) training and b, d) control groups at baseline and at 3 months. V'_E: minute ventilation.

Parameters related to RCP are reported in patients only, in which RCP was identified at baseline and after 3 months.

Exercise oscillatory ventilation definition and measurement of its magnitude

For the definition of EOV (fig. 1), we chose the criteria described by LEITE *et al*. [4], as follows: 1) at least three oscillatory fluctuations in V'_E during warm-up and exercise; 2) regular oscillations, as defined by a standard deviation of three consecutive cycle length durations (time between two consecutive nadirs) within 20% of the average; and 3) a minimal average ventilation amplitude of $\geqslant$5 L, defined as peak V'_E of one oscillation minus the average of two adjacent nadirs.

To evaluate the change of EOV magnitude from baseline to follow-up, two time periods, during unloaded cycling and during the ramp protocol, were analysed. EOV magnitude during warm-up was determined by calculating the variation coefficient of V'_E, *i.e.* the standard deviation of breath by breath V'_E, divided by mean V'_E (fig. 1). To account for the response of V'_E to increasing workload, EOV magnitude during the ramp protocol was evaluated by the correlation coefficient of V'_E, *i.e.* how much do V'_E variations of oscillatory breathing deviate from the linear V'_E regression line (fig. 1)?

To correlate changes in V'_E oscillations after exercise training with CPET parameters, the amplitude of oscillatory ventilation of the first three regular oscillations at the beginning of incremental exercise was used.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA). Mean$\pm$SD values are reported for key variables. Categorical variables were analysed by the Chi-squared test. Comparisons of means within a group and between groups at baseline were made by ANOVA. Comparisons of changes from baseline to follow-up between groups were made after adjustment for baseline values as well by ANOVA. Pearson's correlation coefficient was used for appropriate associations between exercise parameters. The level of statistic significance was set at a two-tailed probability value of $p<0.05$.

RESULTS

Table 1 shows the medication at baseline and at follow-up. There were no differences in baseline characteristics between the two groups.

After exercise training, mean$\pm$SD left ventricular ejection fraction improved from 27.3$\pm$8.9% to 34.2$\pm$10.1% in the training group ($p<0.001$), whereas no change was observed in the control

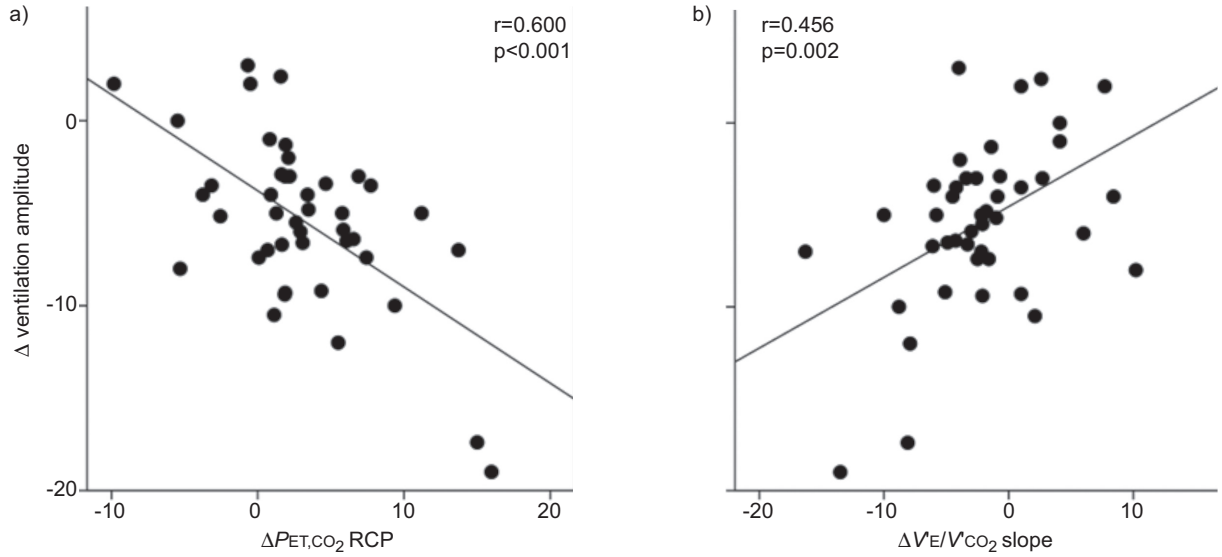

FIGURE 3. Correlation between change in amplitude of oscillatory ventilation after exercise training and a) change in end-tidal carbon dioxide tension ($\Delta P_{ET,CO_2}$) at respiratory compensation point (RCP) and b) change in minute ventilation/carbon dioxide production ($\Delta V'_E/V'_{CO_2}$) slope. RCP data are based on 43 out of 52 patients.

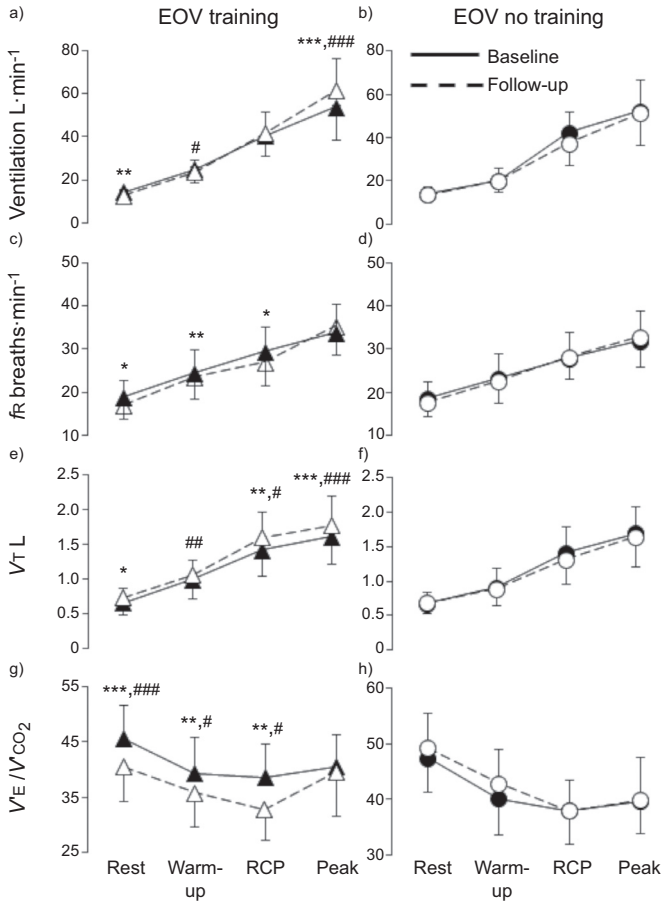

FIGURE 4. Breathing patterns at baseline (solid symbols) and 3 months follow-up (empty symbols) in exertional oscillatory ventilation (EOV) a, c, e and g) training (triangles) and b, d, f, and h) control (circles) patients at rest, end of warm-up, respiratory compensation point (RCP) and peak exercise. RCP data are based on 43 out of 52 patients in the training group and 31 out of 44 patients in the control group. a, b) Ventilation; c, d) respiratory frequency (f_R); e, f) tidal volume (V_T) and g, h) minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$ baseline *versus* follow-up, intra-group comparison; #: $p<0.05$; ##: $p<0.01$; ###: $p<0.001$: comparison of changes from baseline to follow-up between EOV training and control group, adjusted for the baseline values.

group (26.7±8.7% *versus* 26.3±8.6%, p=0.778). Left ventricular end-diastolic diameter did not change in either group (-1.6± 6.8 mm in the training group, p=0.419; -0.5±7.6 mm in the control group, p=0.630).

Ventilatory pattern

EOV disappeared in 37 (71.2%) out of 52 patients after training and only in one (2.3%) out of 44 in the control group ($p<0.001$). In training patients, the amplitude of oscillatory ventilation decreased as reflected by the diminution of the variation coefficient of V'_E during constant workload exercise (warm-up) and by the increase of the correlation coefficient of V'_E, which approached 1 during CPET. In the control group, the variation coefficient significantly increased and the correlation coefficient remained unchanged (fig. 2).

EOV and an elevated V'_E/V'_{CO_2} slope >35 are important prognostic factors; for this reason, we analysed the correlation between them and the influence of a high V'_E/V'_{CO_2} slope on the training response in presence of EOV. The decrease of EOV amplitude correlated inversely with changes in the V'_E/V'_{CO_2} slope (fig. 3). In the 37 patients in which EOV disappeared, the V'_E/V'_{CO_2} slope decreased significantly from 35.5±5.7 to 32.2±6.1 (p=0.002), whereas in the patients with persisting EOV, the V'_E/V'_{CO_2} slope remained unchanged (35.6±6.8 *versus* 33.0±5.8, p=0.132). However, the presence of a V'_E/V'_{CO_2} slope >35 was not predictive of a positive effect of exercise training on EOV: in 23 out of 52 patients with a V'_E/V'_{CO_2} slope >35, EOV disappeared in 15 (65%), whereas in the other 29 patients, EOV disappeared in 22 (76%) patients (p=0.296).

Figure 4 summarises the detailed analysis of breathing patterns at baseline and after 3 months. There were no significant differences in baseline respiratory parameters at rest and during exercise between the two groups. In the training group, resting values of V'_E, f_R and V'_E/V'_{CO_2} ratio decreased significantly and V_T increased significantly (fig. 4). During exercise, V'_E and V_T reached significantly higher values at the peak. The f_R and V'_E/V'_{CO_2} ratio were significantly lower at submaximal exercise but not at maximum exercise. The control patients showed no change in any of these parameters after 3 months.

Exercise capacity

At baseline, patients in the training and control groups did not differ in exercise capacity (table 2) and showed a wide range in peak V'_{O_2} (median 9.6–29.9 mL·kg^{-1}·min^{-1}, interquartile range 13.3–18.9 mL·kg^{-1}·min^{-1}.). Patients undergoing training improved peak workload and peak V'_{O_2}, whereas patients of the control group showed no change in exercise performance after 3 months. No difference in baseline peak V'_{O_2} was present between those in which EOV disappeared after training (16.4±3.4 mL·kg^{-1}·min^{-1}) and those in which it did not (17.1±4.5 mL·kg^{-1}·min^{-1}, p=0.436). However, patients in whom EOV disappeared improved their exercise tolerance (*i.e.* V'_{O_2} by 2.1±3.1 mL·kg^{-1}·min^{-1}), while those who did not lose the EOV pattern showed little change in peak V'_{O_2} (0.8±4.2 mL·kg^{-1}·min^{-1}) after training.

As the persistence or nonpersistence of EOV throughout the whole CPET may influence exercise capacity [15], we analysed the relationship between the EOV pattern at baseline on the response to training. EOV persisted during CPET in 81% of the training and 80% of the control group patients. No significant influence of EOV persistence or nonpersistence was noted in respect to the change of exercise capacity (change (Δ) exercise capacity 14.6±19.2 *versus* 15.0±20.7 W, p=0.491) or oxygen uptake (Δ peak V'_{O_2} 1.6±3.6 *versus* 2.5±2.2 mL·kg^{-1}·min^{-1}, p=0.148) after training.

RCP could be identified in 43 (82.6%) cases from the training and 31 (70.4%) cases from the control group.

DISCUSSION

Our study shows that EOV in CHF patients decreases or even disappears with exercise training. The main change noted in the EOV breathing pattern was a substantial reduction in f_R and an increase in V_T. The decrease of EOV amplitude correlated inversely with changes in P_{ET,CO_2} at RCP, and changes in the V'_E/V'_{CO_2} slope, reflecting ventilatory efficiency.

Patients participating in the exercise training programme were clinically stable and medically optimally treated, meaning that all

TABLE 2 Cardiopulmonary exercise parameters at baseline and follow-up

	EOV training		EOV control	
	Baseline	3 months	Baseline	3 months
Subjects n	52		44	
At rest				
f_C beats·min^{-1}	74±12	70±11*	74±16	73±1
SBP mmHg	105±19	106±18	107±14	105±17
DBP mmHg	66±11	66±10	66±13	64±9
P_{ET,CO_2} mmHg	30.7±3.75	33.0±3.4**	31.7±4.5	32.0±4.8
V_T L	0.66±0.17	0.72±0.15*	0.69±0.14	0.69±0.14
f_R breaths·min^{-1}	19.0±3.9	17.2±3.1*	18.7±3.9	17.7±4.1
V'_E L·min^{-1}	14.3±3.7	12.5±3.1**,#	13.8±2.9	13.5±2.8
V'_E/V'_{CO_2}	45.6±6.0	40.5±6.2***,##	47.8±8.1	49.1±10.3
At maximal exercise and RCP¶				
f_C bpm	115±21	118±20	119±24	122±25
SBP mmHg	126±26	137±28	136±22	136±27
DBP mmHg	67±10	73±10	71±12	66±12
Exercise capacity W	80±20	95±30***,###	86±23	88±26
P_{ET,CO_2} at RCP¶ mmHg	32.4±3.7	36.1±5.9**	32.6±3.8	33.0±3.8
V_T L	1.62±0.39	1.78±0.42***,###	1.69±0.42	1.66±0.40
f_R L·min^{-1}	33.7±6.9	35.5±6.9	32.0±6.5	32.3±7.7
V'_E L·min^{-1}	53.5±14.6	61.3±14.8***,###	52.0±11.8	51.3±10.7
V'_E/V'_{CO_2} slope up to RCP	34.9±5.4	32.1±5.6**	33.7±6.3	33.0±6.7
V'_{O_2} mL·kg^{-1}·min^{-1}	16.5±3.6	18.3±4.4**,#	16.2±4.6	16.3±3.6

Data are presented as mean±SD, unless otherwise stated. EOV: exertional oscillatory ventilation; f_C: cardiac frequency; SBP: systolic blood pressure; DBP: diastolic blood pressure; P_{ET,CO_2}: end-tidal carbon dioxide tension; V_T: tidal volume; f_R: respiratory frequency; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; V'_{O_2}: oxygen uptake; RCP: respiratory compensation point. *: p<0.05; **: p<0.01; ***: p<0.001 for baseline *versus* follow-up, intra-group comparison; #: p<0.05; ##: p<0.01; ###: p<0.001 for comparison of changes from baseline to follow-up between EOV training and control group, adjusted for the baseline values. ¶: RCP data based on 43 patients in the training group and 31 patients in the control group.

patients had an angiotension-converting enzyme (ACE)-inhibitor or an angiotensin receptor blocker (ARB), 90% were receiving a β-blocker and 80% of the patients were receiving diuretics. In the control group, the percentage of patients receiving ACE inhibitors or ARBs and β-blockers was somewhat smaller. However, the number receiving diuretics, which are known to influence EOV, was equal. Importantly, changes in medication over 3 months are minor, meaning that the effects observed on EOV were not influenced by a change of medication.

It is also noteworthy that EOV was present within a wide range of peak V'_{O_2}, with some of the patients having achieved a peak V'_{O_2} >20 mL·kg^{-1}·min^{-1}. This shows that EOV might be detected in an extensive spectrum of heart failure patients, thus confirming a study by OLSEN *et al*. [16] who reported the occurrence of EOV in 19 (41%) out of 47 patients with an ejection fraction ⩾40%.

Several exercise-induced mechanisms might account for the favourable influence of exercise training on EOV. Exercise training has consistently been shown to improve central haemodynamic performance [17], and improvements of cardiac output by cardiac pacing [18] or resynchronisation [19] have been shown to reduce or abolish an oscillatory ventilatory pattern. Interestingly, recent studies support the notion of a haemodynamic basis for EOV and advocate EOV as an easily recognisable surrogate for exercise haemodynamics. MURPHY *et al*. [20] showed that EOV indicates an inadequate haemodynamic response to exercise in terms of impaired increase of cardiac index, increased filling pressures and augmented reliance on oxygen extraction. Furthermore, treatment with sildenafil, a highly selective phosphodiesterase-5 inhibitor, is able to reverse EOV in proportion to improvements in cardiac output [20, 21], which confirms an earlier observation with milrinone, another phosphodiesterase inhibitor [6], and might offer a new therapeutic strategy in EOV patients. Regarding the control of ventilation, various interventions, such as exposure to hyperoxia [9], dynamic administration of carbon dioxide [22] or continuous positive airway pressure [23], have improved periodic breathing during sleep, but also during wakefulness.

In our study, the increase of V_T after exercise training was the most striking change of the respiratory pattern. Two mechanisms might have been responsible for this improvement: an improvement in diaphragmatic muscle performance and a reduction of pulmonary congestion. The former has been reported to occur with aerobic exercise training combined with inspiratory muscle training [7, 24]. Regarding pulmonary congestion, in CHF patients there is a redistribution of pulmonary blood flow to the apices already at rest, resulting in

an inability to increase the proportion of upper zone perfusion during exercise with lower values of P_{ET,CO_2} [25]. The significant increase in P_{ET,CO_2} and decrease in V'_E/V'_{CO_2} slope in our study may indicate an improvement in carbon dioxide delivery to the lungs and a reduction in the ventilation/perfusion mismatch.

The reduction of f_R is more likely to be related to an improvement in respiratory control mechanisms on the level of ergo- [26] and peripheral chemoreceptors [27]. Contrary to normal subjects, in whom ventilation is triggered *via* central chemoreceptors, in CHF patients, lactate may exert its effects *via* intramuscular ergoreceptors before entering the circulation [28]. Local muscle lactic acid accumulation with exercise has been shown in the diaphragm [29] and in the skeletal muscle [28]. This suggests an important role for local muscular acidosis as a stimulus of ergo- and peripheral chemoreceptor reflex activation and hyperventilation. By reducing this abnormal metabolic response, exercise training can suppress the overactive metabolic reflex [26].

The presence of EOV is a strong predictor for reduced survival [3]. Together with other CPET parameters, such as reduced peak V'_{O_2} and elevated V'_E/V'_{CO_2} slope, it characterises patients with the highest mortality risk [30]. The ability to improve these parameters and even reverse EOV with exercise training is a sign of persisting cardiovascular reserve and might discern patients with better prognosis. Those who are unable to respond favourably to exercise training would be candidates for the most aggressive medical (sildenafil) and/or device therapy, or even listing for transplantation.

Limitations

The major limitation of our study is that it was retrospective and training was effectuated in a single centre. Furthermore, analysis of the exercise tests was not blinded. However, the impact of exercise training on the ventilatory parameters is so pronounced that these short comings should have little influence on the main findings of the study.

The reliability of calculation of the V'_E/V'_{CO_2} slope in patients with EOV might be questioned due to the cyclic variation of V'_E and V'_{CO_2} during the stress test. However, we were able to derive the V'_E/V'_{CO_2} slope during all CPETs, since V'_E and V'_{CO_2} both oscillate in the same way, albeit with a small difference in time response.

The effect of detraining was not assessed and therefore the time delay between detraining and EOV reappearance remains unknown.

Conclusion

A 3-month exercise training programme leads to a significant decrease of EOV in patients with stable CHF, characterised mainly by a disappearance of periodicity, decrease in f_R and an improvement in V_T. These changes are associated with improved ventilatory efficiency (V'_E/V'_{CO_2} slope) and evidence of better central haemodynamics during exercise (P_{ET,CO_2} at the RCP). Such beneficial effects were absent in patients not attending an exercise training programme.

STATEMENT OF INTEREST

None declared.

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