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Exercise training reverses exertional oscillatory ventilation in heart failure patients

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ABSTRACT

Background: 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.

Objectives: 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.

Methods: 96 stable CHF patients with EOV were included in a retrospective analysis (52 training vs. 44 controls). EOV was defined as follows: (1) ≥3 oscillatory fluctuations in V_E during exercise; (2) regular oscillations; (3) minimal average ventilation amplitude ≥5 litres.

Results: EOV disappeared in 37/52 (71.2%) patients after training but only in 1/44 (2.3%) without training ($p<0.001$). The decrease of EOV amplitude correlated with changes in $P_{ET}CO_2$ ($r=-0.60$, $p<0.001$) at the respiratory compensation point (RCP) and V_E/VCO_2 slope ($r=0.50$, $p<0.001$). Training significantly improved resting values of breathing frequency (BF), ventilation (V_E), tidal volume (V_T) and V_E/VCO_2 ratio. During exercise, V_E and V_T reached significantly higher values at the peak, while BF and V_E/VCO_2 ratio were significantly lower at submaximal exercise. No change was noted in the control group.

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

Key words: cardiopulmonary exercise test, congestive heart failure, exercise training, oscillatory ventilation, periodic breathing, rehabilitation

INTRODUCTION

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 (V_E/V_{CO_2} slope) are traditionally considered the strongest predictors [2], but exertional oscillatory ventilation (EOV) has recently emerged as new index linked with poor prognosis [3-5].

EOV consists of cyclic hyper- and hypopnea, characterised by an oscillatory kinetic in V_{O_2} and carbon dioxide output (V_{CO_2}), with a period that varies from 45 to 90 sec. It has been reported to occur in 12 to 30% of CHF patients during CPET [3, 4], depending on the severity of the disease. Until now, reports on patients with EOV have mainly focussed 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 hemodynamic 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 are postulated in the genesis of EOV. The ventilatory hypothesis assumes an instability of breathing control due to abnormal chemoreceptor's feedback [8-10], whereas reduced cardiac output or cardiac output fluctuations constitute the hemodynamic hypothesis of EOV occurrence [11-14].

Aerobic endurance training in CHF patients improves ventilatory efficiency, central hemodynamic factors and peripheral muscle chemoreflex response, which are all implicated in the genesis of EOV. We hypothesised that an aerobic 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 hemodynamic parameters in 96 stable CHF patients with EOV, 52 patients undergoing a 3 month outpatient exercise training programme and 44 patients serving as a control. It is a retrospective analysis of data derived from the outpatient cardiac rehabilitation clinic at the University Hospital 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% und were in stable clinical condition. An incremental symptom limited CPET on a cycle ergometer was performed at baseline and after three months of training or control phase. Patients with angina or signs of myocardial ischemia, relevant obstructive lung disease (Tiffeneau ratio <70% and FEV_1 <60% predicted) or reduced vital capacity (<60% of predicted value), congenital heart disease with 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 3 times a week for a period of 3 months. The programme included 36 exercise and 12 information sessions. Each training session consisted of 2 units of 45 minutes, composed mainly of aerobic endurance training performed on a cycle ergometer and in form of callisthenic exercises. Training intensity was set between 60-80% of peak VO_2, determined by a preliminary CPET.

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 Vivid 7, GE, US) and CPET. Before exercise testing, a 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), Oxycon Alpha®, Jaeger-Toennies, Höchberg, Germany, was used in the laboratory in Bern, Vmax 29C, SensorMedics,

USA in the laboratories in Veruno and Piacenza. Acquisition of resting data was followed by an unloaded cycling warm-up period up to 3 minutes. Thereafter, a personalized ramp protocol was used for each patient, with the objective to reach maximum exercise capacity within 8 to 12 min.

Values of ventilation (V_E), breathing frequency (BF) and tidal volume (VT) at rest and during warm-up are reported as averages obtained over 60 seconds (the last 60 seconds during warm-up), whereas the values at the respiratory compensation point (RCP) and at peak exercise were averaged over 30 seconds. Resting end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) was collected for 60 seconds prior to exercise in the seated position, whereas the value at the RCP was averaged over 30 seconds. Peak VO_2 was computed as the 60 seconds average values of VO_2 during the last stage of the exercise test. The slope of minute ventilation vs. carbon dioxide output (V_E/VCO_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 non-linear rise in V_E occurred relative to VCO_2; and (2) the continuous decrease of $P_{ET}CO_2$ following it's peak. 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 (Figure 1), we chose the criteria described by Leite et al. [4]: (1) at least three or more oscillatory fluctuations in V_E during warm-up and exercise; (2) regular oscillations, as defined by a standard deviation (SD) of 3 consecutive cycle length durations (time between 2 consecutive nadirs) within 20% of the average; (3) a minimal average ventilation amplitude of at least 5 litres, 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 analyzed. EOV magnitude during warm-up was determined by calculating the *variation* coefficient of V_E, i.e. the SD of breath by breath V_E, divided by mean V_E (Figure 1). To account for the response of V_E to increasing workload, EOV magnitude during 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 (Figure 1).

To correlate changes in V_E oscillations after exercise training and 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 the SPSS® for Windows® software (version 15.0, SPSS® Inc., Chicago, Illinois, USA). Mean values ± SD are reported for key variables. Categorical variables were analysed by the Chi-square test. Comparison of means within a group and between groups at baseline were made by analysis of variance (ANOVA). Comparisons of changes from baseline to follow-up between groups were made after adjustment for baseline values as well by ANOVA test. Pearson`s correlation coefficient was used for appropriate associations between exercise parameters. The level of statistic significance was set at a 2-tailed probability value <0.05.

RESULTS

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

After exercise training, left ventricular ejection fraction improved from 27.3±8.9% to 34.2±10.1% in the training group ($p<0.001$), whereas no change was observed in the control group (26.7±8.7% vs. 26.3±8.6%, $p=0.778$). LVEDD did not change in both groups (-1.6±6.8 mm in the training, $p=0.419$; -0.5±7.6 mm in the control group, $p=0.630$).

Ventilatory pattern

EOV disappeared in 37/52 (71.2%) patients after training and only in 1/44 (2.3%) 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 (Figure 2).

EOV and an elevated V_E/VCO_2-slope > 35 are important prognostic factors for which reason we analysed the correlation between them and the influence of a high V_E/VCO_2-slope on the training response in presence of EOV. The decrease of EOV amplitude correlated inversely with changes in the VE/VCO2-slope (Figure 3). In the 37 patients in which EOV disappeared, V_E/VCO_2-slope decreased significantly from 35.5± 5.7 to 32.2±6.1 ($p=0.002$) whereas in the patients with persisting EOV, V_E/VCO_2-slope remained unchanged (35.6±6.8 vs. 33.0±5.8, $p=0.132$). However, the presence of a V_E/VCO_2-slope > 35 was not predictive of a positive effect of exercise training on EOV: in 23/52 patients with a V_E/VCO_2-slope > 35, EOV disappeared in 15 (65%), whereas in the other 29 patients, EOV disappeared in 22 patients (76%)($p=0.296$).

Figure 4 summarizes 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, BF, and

V_E/VCO_2 ratio significantly decreased and V_T significantly increased (Table 2). During exercise, V_E and V_T reached significantly higher values at the peak. BF and V_E/VCO_2 ratio were significantly lower at sub-maximal exercise but not at maximum. The control patients showed no change in any of these parameters after 3 months.

Exercise capacity

At baseline, patients of the training and control group did not differ in exercise capacity (Table 2) and showed a wide range in peak VO_2 (9.6-29.9 ml/kg/min., interquartile range: 13.3-18.9 ml/kg/min.). Patients undergoing training improved peak work load and peak VO_2, whereas patients of the control group showed no change in exercise performance after 3 months. No difference in baseline peak VO_2 was present between those in which EOV disappeared after training (16.4±3.4 ml/kg/min) and those in which it did not (17.1±4.5 ml/kg/min, p=0.436). However, patients in whom EOV disappeared improved exercise tolerance (i.e. VO_2 by 2.1±3.1 ml/kg/min), while those who did not lose the EOV pattern, showed little changes in peak VO_2 (0.8±4.2 ml/kg/min) after training.

Since the persistence or non-persistence of EOV throughout the whole CPET may influence exercise capacity [15], we analysed the relation 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 non-persistence was noted in respect to the change of exercise capacity (Δ watt 14.6±19.2 vs. 15.0±20.7, p=0.491) or oxygen uptake (Δ peak VO_2 1.6±3.6 vs. 2.5±2.2 ml/kg/min, p=0.148) after training.

RCP could be identified in 43 (82.6%) cases of the training and 31 (70.4%) cases of 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 of BF and an

increase in V_T. The decrease of EOV amplitude correlated inversely with changes of $P_{ET}CO_2$ at RCP, and changes in the V_E/VCO_2-slope, reflecting ventilatory efficiency.

Patients participating in the exercise training programme were clinically stable and medically optimal treated, meaning that all patients had an ACE-inhibitor or an angiotensin receptor blocker (ARB), 90% were on a beta-blocker and 80% of the patients were on diuretics. In the control group, the percentage of patients on ACE-Inhibitors or ARB's and beta-blockers was somewhat smaller. However, the number on diuretics, known to influence EOV, was equal. Importantly, changes of medication over 3 months was minor, meaning that the effects observed on EOV were not influenced by medication.

It is also noteworthy that EOV was present within a wide range of peak VO_2, some of them having achieved a peak VO_2 greater than 20ml/kg/min. This documents, that EOV might be detected in an extensive spectrum of heart failure patients, confirming thus a study by Olsen et al. [16] who reported the occurrence of EOV in 19/47 patients (41%) with an ejection fraction ≥40%.

Several exercise induced mechanisms might account for the favourable influence of exercise training on EOV. Exercise training has consistently shown to improve central hemodynamic performance [17] and improvements of cardiac output by cardiac pacing [18] or resynchronization [19] have been shown to reduce or abolish an oscillatory ventilatory pattern. Interestingly, recent studies support the notion of a hemodynamic basis for EOV and advocate EOV as an easily recognizable surrogate for exercise hemodynamics. [20] Murphy et al. showed that EOV indicates an inadequate hemodynamic 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 like exposure to hyperoxia [9], dynamic administration of CO_2 [22] or continuous positive airway pressure [23] have been able to improve periodic breathing during sleep, but also awake.

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 of $P_{ET}CO_2$ and decrease of VE/VCO_2 slope in our study may indicate an improvement in CO_2 delivery to the lungs and the reduction in ventilation/ perfusion mismatch.

The reduction of BF is more probably 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 the 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 like reduced peak VO_2 and elevated V_E/VCO_2 slope, it characterizes 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 the study is, that it was retrospective and training was effectuated in a single centre. Furthermore the 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 had little influence on the main findings of the study.

The reliability of calculation of the V_E/VCO_2-slope in patients with EOV might be questioned due to the cyclic variation of V_E and VCO_2 during the stress test. However we were able to derive the VE/VCO2 slope during all CPETs, since V_E and VCO_2 oscillate both in the same way even though 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 BF and an improvement in V_T. These changes are associated with improved ventilatory efficiency (V_E/VCO_2 slope) and evidence of better central hemodynamics during exercise ($P_{ET}CO_2$ at the RCP). Such beneficial effects were absent in patients not attending an exercise training programme.

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TABLES

Table 1. Patient characteristics

	EOV Training n=52	**EOV Control n=44**	**p-value**
Age, years	58±10	59±13	0.413
Gender, M/F	47/5	39/5	0.780
BMI, kg/m^2	26.1±4.6	25.9±4.4	0.961
Etiology, ischaemic/ non-ischaemic	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-I's or ARB's	52 (100%)	42 (96%)	0.120
Beta-blockers	47 (90%)	33 (75%)	0.056
Diuretics	42 (81%)	36 (82%)	0.779
Medication at follow-up			
ACE-I's or ARB's	52 (100%)	42 (96%)	0.120
Beta-blockers	48 (92%)	34 (77%)	0.046
Diuretics	43 (83%)	36 (82%)	0.424

ACE-I's = angiotensin converting enzyme inhibitors; ARB's = angiotensine receptor blockers; BMI = body mass index; EOV= exertional oscillatory ventilation;, LVEF = left ventricular ejection fraction; LVEDD = left ventricular enddiastolic diameter, M/ F= male/ female

Table 2. Cardiopulmonary exercise parameters at baseline and follow-up

	EOV Training n = 52		EOV Control n = 44	
	baseline	3 months	baseline	3 months
At rest				
HR, bpm	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
BF, 1/min.	19.0±3.9	17.2±3.1*	18.7±3.9	17.7±4.1
V_E, l/min.	14.3±3.7	12.5±3.1$^{**, \#}$	13.8±2.9	13.5±2.8
V_E/VCO_2	45.6±6.0	40.5±6.2$^{***, \#\#}$	47.8±8.1	49.1±10.3
At maximal exercise and RCP†				
HR, 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
$P_{ET}CO2$ 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
BF, l/min	33.7±6.9	35.5±6.9	32.0±6.5	32.3±7.7
V_E, l/min	53.5±14.6	61.3±14.8$^{***, \#\#\#}$	52.0±11.8	51.3±10.7
V_E/VCO_2 slope up to RCP	34.9±5.4	32.1±5.6**	33.7±6.3	33.0±6.7
VO_2, ml/kg/min.	16.5±3.6	18.3±4.4$^{**, \#}$	16.2±4.6	16.3±3.6

BF = breathing frequency; bpm = beats per minute; DBP = diastolic blood pressure; EOV = exertional oscillatory ventilation; RCP = respiratory compensation point; RER = respiratory exchange ratio; SBP = systolic blood pressure; V_T = tidal volume, V_E = ventilation.

* p<0.05, ** p<0.01, *** p<0.001: baseline vs. follow-up, intragroup 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.

†RCP data based on 43 patients in training and 31 patients in control group.

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FIGURES:

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) 4 or more regular oscillations; (2) regular oscillation, defined as a standard deviation of 3 consecutive cycle lengths (time between two consecutive nadirs) within 20% of the average; (3) a minimal average amplitude of at least 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.

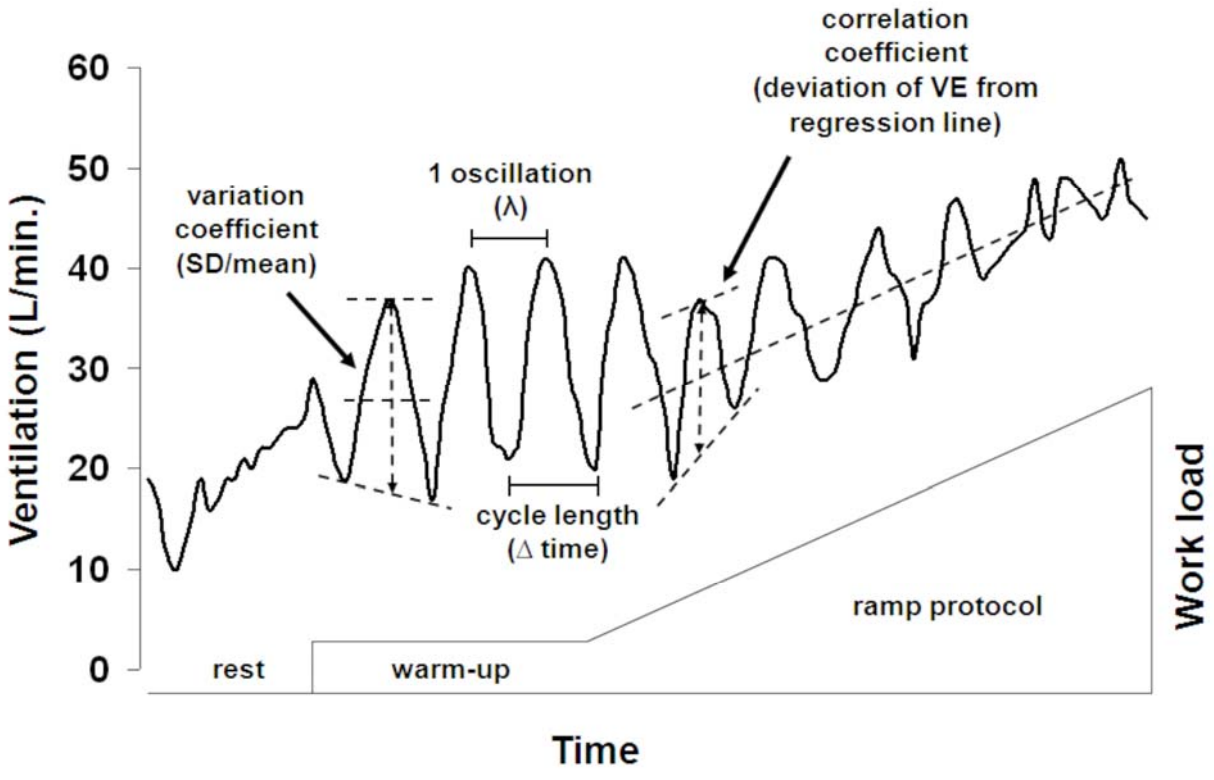


Figure 2: Variation coefficient and correlation coefficient in the EOV training and control group at baseline and at 3 months.

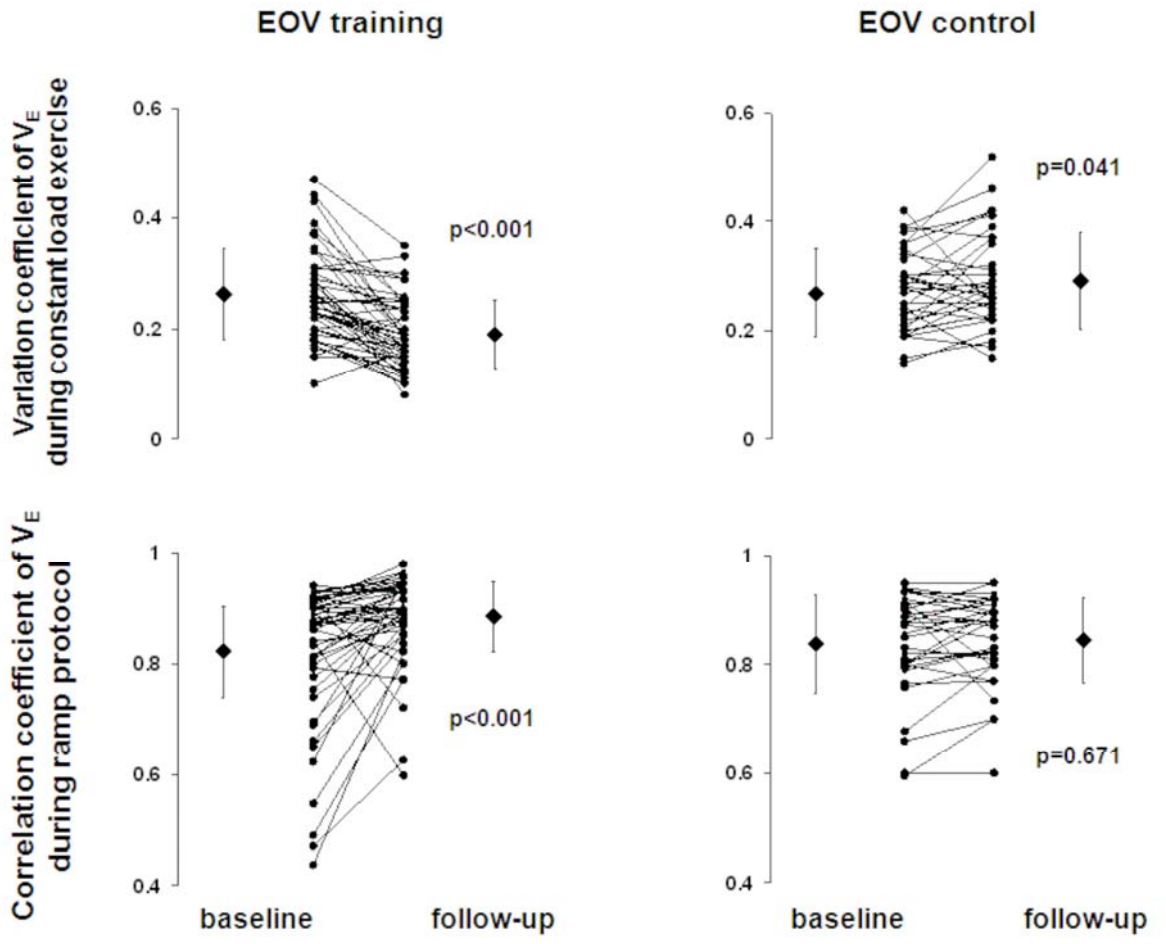


Figure 3: Correlation between change in amplitude of oscillatory ventilation after exercise training and change in $P_{ET}CO_2$ at RCP and V_E/VCO_2 slope. RCP data based on 43/52 patients.

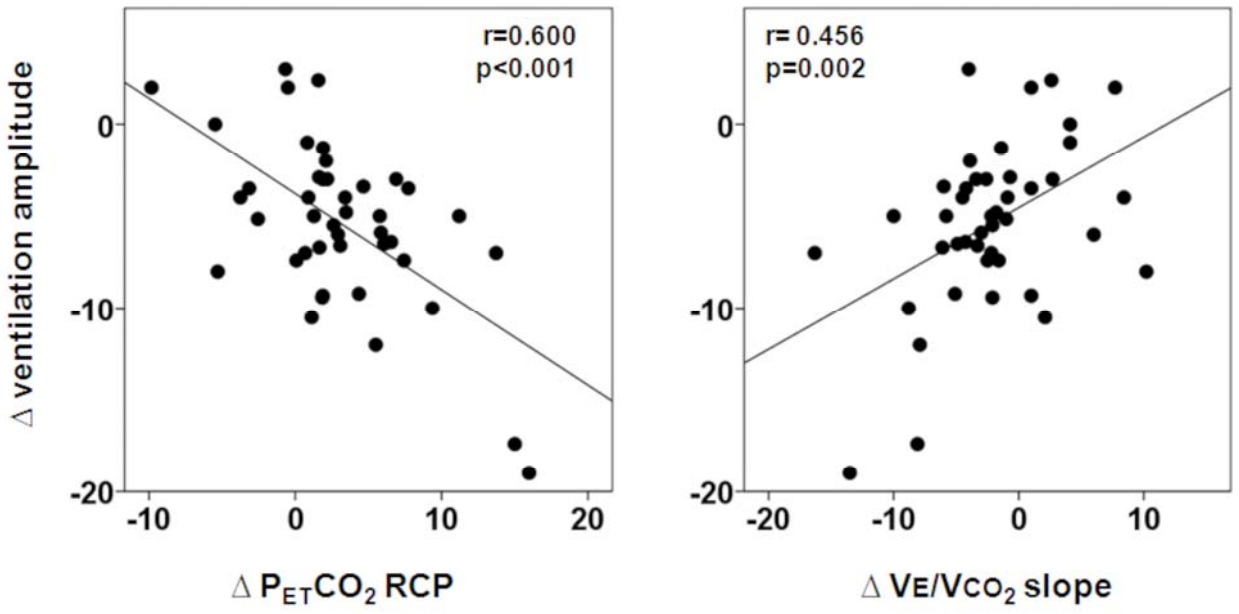
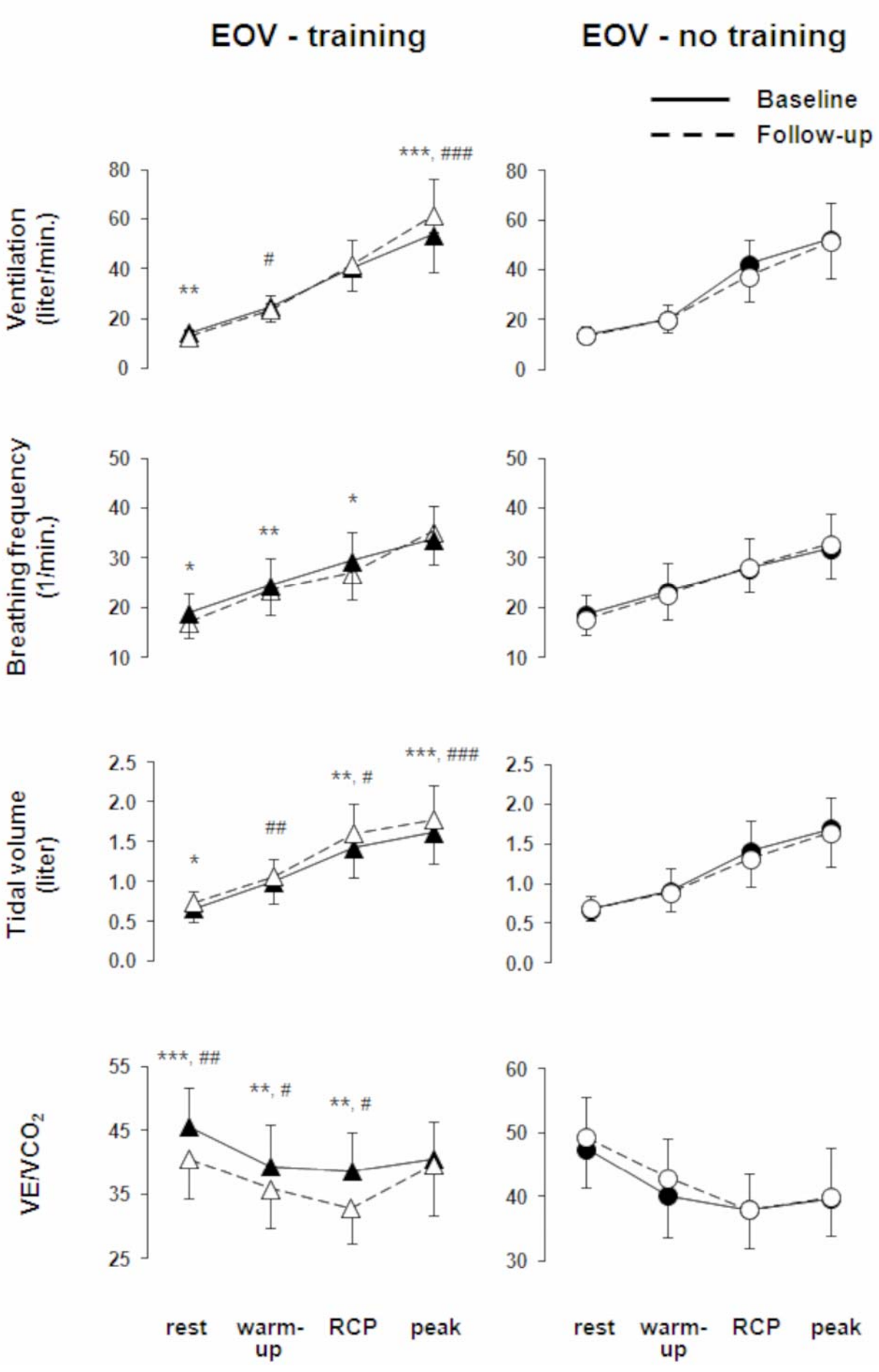


Figure 4: Breathing patterns at baseline and 3 months follow-up in EOV training and control patients at rest, end of warm up, RCP and peak exercise. RCP data based on 43/52 patients in the training group and 31/44 patients in the control group.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ baseline vs. follow-up, intragroup 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.


EOV - training
EOV - no training
Baseline
Follow-up
Ventilation (liter/min.)
Breathing frequency (1/min.)
Tidal volume (liter)
VE/VCO2
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rest
warm-up
RCP
peak