Different training modalities to improve exercise tolerance in COPD and a new technique for detection of airflow limitation related to exercise intolerance

Ph.D. Thesis

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Szeged

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2010

LIST OF ARTICLES AND ABSTRACTS RELATED TO THE SUBJECT OF THE DISSERTATION

Peer reviewed publications:

I. **Varga J,** Boda K**,** Somfay A: Kontrollált és otthoni (nem kontrollált) dinamikus tréning COPD-s betegek rehabilitációjában.Orv. Hetil. 2005; 146:2249-2255.

II. **Varga J,** Porszasz J, Boda K, Casaburi R, Somfay A**:** Supervised high intensity continuous and interval training vs. self-paced training in COPD. Respir. Med. 2007; 101(11):2297-304., **IF: 2.235**

III. **Varga J,** Porszasz J, Boda K, **C**asaburi R, Somfay A**:** Felügyelt magas intenzitású folyamatos és intervallum, valamint otthoni tréning hatásának vizsgálata krónikus obstruktív tüdőbetegek rehabilitációjában. Med. Thor. 2008; 61(1): 135-143.

IV. Ma S, Hecht A, **Varga J**, Rambod M, Morford S, Goto S, Casaburi R, Porszasz J: Breath-by-breath assessment of progressive airflow limitation during exercise in COPD: a new method. Respir. Med. 2010; 104: 389-396., **IF: 2.338**

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I. **Varga J**: Kontrollált és otthoni (nem kontrollált) dinamikus tréning COPD-s beteget rehabilitációjában. Fiatalok Tudományos Fóruma, XII. Cserháti István Emlékülés, Szeged, 2003. 39. p.

II. **Varga J,** Somfay A: Kontrollált és otthoni (nem kontrollált) dinamikus tréning COPD-s betegek rehabilitációjában. Magyar Tüdőgyógyász Társaság 53. Nagygyűlése, Debrecen, 2004. 20.p.

III. Barnai M, Domján A, **Varga J,** Somfay A. Az állóképesség fejleszthetősége idős korban. Magyar Gerontológiai Társaság Kongresszusa, Szeged, 2004. március 26-27.

IV. **Varga J,** Boda K, Somfay A: Folyamatos (kontrollált vs. nem kontrollált) és intervallum dinamikus tréning COPD-s betegek rehabilitációjában. A Magyar Tüdőgyógyász Társaság Allergológiai és Légzéspathológiai szekciójának tudományos ülése, Balatonfüred, 2005.10. p.

V. Barnai M, Domján A, **Varga J,** Somfay A, Jeney K, Sárga N, Verebély B, Horváth Gy: Az akaratlagos apnoe idő és a nyolcvan évesek állóképességének vizsgálata. Magyar Élettani Társaság LXIK. Vándorgyűlése, Budapest, 2005. június 2-4.

VI. **Varga J,** Boda K, Somfay A: Comparison of controlled and uncontrolled lower extremity training in the rehabilitation of patients with chronic obstructive pulmonary disease. European Respiratory Society Anual Meeting, Copenhagen, Eur Respir J 2005; 26: Suppl. 49, 70s.

VII. **Varga J,** Porszasz J, Boda K, Casaburi R, Somfay A: Effectiveness of supervised high intensity continuous and interval training compared with self-controlled exercise training in COPD. American Thoracic Society Annual Meeting, San Diego, May 20-24, 2006, 3: A 813.

VIII. **Varga J,** Shuyi M, Hecht A, Hsia D, Casaburi R, Porszasz J: Detection of Dynamic Airway Compression during Exercise in COPD by Breath by Breath Analysis of Spontaneous Flow-Volume Loops. European Respiratory Society Annual Meeting, Sep 2-6, 2006, ERS Supplemenet: 204s: P1224

IX. Barnai M, Domján A, **Varga J,** Somfay A, Nagy E, Horváth Gy: Exercise capacity of the 80 age-old people. microCAD. 2006 International Scientific Conference, Miskolc, 2006. marcius 16-17.

X. **Varga J,** Ma S, Hecht A, Hsia D, Somfay A, Casaburi R, Porszasz J: Dinamukis légúti kompresszió és dinamikus hyperinfláció vizsgálata COPD-ben és egészségesekben. A Magyar Tüdőgyógyász Társaság 55. Nagygyűlése, Balatonfüred, 2008, P 185.

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List of Abbreviations

COPD	Chronic obstructive pulmonary disease
EFL	Expiratory flow limitation
NEP	Negative expiratory pressure
SEFV	Spontaneous expiratory flow-volume curve
VE	Minute ventilation
MVV	Maximal voluntary ventilation
FEV_1	Forced expiratory volume in one second
ATS	American Thoracic Society
ERS	European Respiratory Society
W	Watt
rpm	Rate per minute
$\dot{V}_E$	Pulmonary ventilation
$\dot{V}O_2$	Oxygen uptake
$\dot{V}CO_2$	Carbon-dioxide output
LAT	Lactic acidosis threshold
SpO2	Oxygen saturation
$\dot{V}_E / \dot{V}CO_2$	Ventilatory equivalent for CO_2
f	Respiratory rate
HR	Heart rate
ECG	Elektrocardiogram
GE	General Eletric
C group	Supervised continuous training group
I group	Supervised interval training group
S group	Self-paced training group
A/D converter	Analog/digital converter
RAR	Rectangular area ratio
$\dot{V}_{max}$	Maximum spontaneous expiratory flow
$\dot{V}_{EE}$	End-expiratory flow

$\dot{V}O_{2peak}$	Maximal oxygen uptake
SD	Standard deviation
BMI	Body mass index
FVC	Forced vital capacity
TLC	Total lung capacity
FRC	Functional residual capacity
RV	Residual volume
D_LCO	Diffusion capacity of carbon monoxide
PaO_2	Arterial partial oxygen pressure
$PaCO_2$	Arterial partial carbon-dioxide pressure
SE	Standard error
PWR	Peak work rate
ANOVA	Analysis of Variance

Introduction

Pulmonary rehabilitation is an integrative part of management of patients with chronic obstructive pulmonary disease (COPD). Randomized, controlled trials showed as an evidence that exercise training improves exercise capacity and quality of life in COPD (1). Breathlessness and peripheral muscle dysfunction are the pri mary reasons for decreased ability to perform normal activities and reduce quality of life (1). Exercise training has favorable effects on breathing, circulation and metabolism (2). These physiologic effects depend on training frequency, intensity, modality, and duration (3-9).

The aim of several research groups was to determine the relative effectiveness of interval training (higher intensity alternated with lower intensity periods) compared to constant work rate (continuous) exercise training. In healthy subjects some (10, 11), but not all (12-14), studies have showed superior effect in selected physiologic parameters in interval vs. continuous training. In COPD, two studies have not found differences between these training strategies (4, 8). Ambrosino reviewed studies about interval training and has found that it leads to higher physiologic benefit in peak oxygen consumption and peak work rate, a greater improvement in lactate threshold, and this type of training is more easily accepted, especially in elderly people (15). It was concluded that in COPD patients, there were no exact results about the superiority of high intensity bilevel interval training (15). There might be some controversy in the effectiveness of self-paced training programs. While these programs have favourable effects, like improved exercise capacity, reduced breathlessness and improved quality of life (9), the relative influence of this training modality compared to supervised training programs remains unclear (6, 7).

Exercise intolerance is one of the principal determining factor in quality of life, especially in advanced stages of COPD (16). Reduced ventilatory capacity can have large impact in exercise intolerance in patients with severe COPD, mainly affected by expiratory flow limitation (EFL) related to elevated airway resistance and decreased elastic recoil (17-20).

The main element of EFL is increased airway resistance as it leads a series of changes in other modulators of airflow (21). Increased intrathoracic pressure is generated because the rise in resistance leads to prolonged time constants of the airways, and higher pressure is needed to drive flow (22). Higher pressure results in increased gas compression and dynamic

airway compression in the airways (23-25). All of these components result in intrabreath reduction of flow (17, 19, 23-25) presenting in a concave shape on the expiratory flow-volume curve – as an indication of flow falling quickly after expiration starts.

Several methods have sought to evaluate EFL during exercise (26-30). One method has the advantage of the fact that EFL achieves the point when expiratory flow turns to independent of driving pressure, i.e. the flow does not increase when negative expiratory pressure (NEP) is applied at the mouth (28). Forced oscillation technique is another way to detect EFL, which is based on the concept that oscillatory pressure cannot pass through flow-limiting airway segments, the consequences of this phenomenon are reduced apparent compliance and respiratory system input reactance (29). Although both NEP and forced oscillation techniques offer a reliable method to quantify EFL during spontaneous breathing, the implementation of either method is a methodical challenge and even if successful has limitations because both methods require cooperation from the subject that can be difficult to achieve during exercise. The forced oscillation technique requires complex instrumentation with a breathing technique that allows a free passage through the oropharynx and glottis (30) and the measurement takes about 20 seconds. The NEP method can only be applied intermittently and the necessitates comparison of expiratory flow profiles with and without the application of NEP (28).

The expiratory limb of the maximal flow-volume loop in a classic forced expiratory spirometry shows concavity in patients with obstructive airway disease and that concavity becomes more prominent with the more seve airflow obstruction. Therefore, we hypothesized that EFL can be assessed *quantitatively* by detecting the configuration of spontaneous expiratory flow-volume (SEFV) curves during rest and exercise on a breath-by-breath basis. This method does not require any change in physiologic breathing pattern or alteration of the usual procedures used in cardiopulmonary exercise testing (31, 32). Relevant information of EFL may be gained from the shape of SEFV curves because, as stated above, changes in the variables related to EFL (i.e. dynamic airway compression, gas compression and the time constants of involved lung compartments) are predictably reflected in intrabreath changes of flow. Moreover, in presence of EFL, flow rates of spontaneous expirations are based on mechanisms similar to those influencing forced expirations (25, 33), which have been considered to be valuable methods to characterize EFL (34-37). This implies that the shape of SEFV curves, especially the degree of its concavity, might be useful to quantify the

augmentation of EFL as exercise gathers and the minute ventilation approaches breathing capacity.

In this methodological part of the thesis our goal was to develop computerized analysis to quantify the configuration of the spontaneous flow-volume profile on a breath-by-breath basis throughout during exercise, with special detection of the development of EFL in moderate to severe COPD patients. To gain a *preliminary* appreciation of the potential of this technique, and before comparing it with the previously mentioned known methods, we also made a comparison between the spontaneous expiratory flow-volume responses in COPD patients and age-matched healthy individuals. In addition, the relation between the degree of SEFV curve concavity and measures of ventilatory limitation during exercise (i.e. VE/MVV) was also investigated.

Aims of the study

Study I.

In Study I we sought determining the relative effectiveness of supervised continuouos, interval and home-based training in COPD. We intended that it would have great practical importance

- to determine whether there were differences in the improvements in exercise tolerance or perceived activity levels between these three training modalities,
- to compare maximal work rate, metabolic profile (gas exchange, lactate threshold), ventilatory and circulatory differences between these groups
- to assess and follow-up symptoms related to quality of life after different rehabilitation programs.

  The results of this study might help to develop practical guidance for rehabilitation professionals seeking to institute effective rehabilitative interventions for patients with COPD.

Study II.

With the intention of continuous, breath by breath monitoring we aimed to develop computerized procedures to quantify the configuration changes of the spontaneous flow-volume curve during exercise in severe COPD patients. Our specific aims were:

- to gain a *preliminary* appreciation of the accuracy of this technique according to the spontaneous expiratory flow-volume responses in a group of COPD patients and a group of age-matched healthy individuals,
- to detect EFL by investigation of the spontanouos flow-volume loops in moderate to severe COPD patients,
- to analyze the comparison of detecting EFL and exercise intolerance of COPD patients.

Materials and Methods

Study subjects

Study I

Seventy-one stable patients with very severe to moderate COPD ((forced expired volume in one second (FEV_1) range: 21-94% pred)) (38) participated in study I; none of them qualified for long-term oxygen therapy. The study was approved by the local ethical committee and the patients gave their written consent to their participation. Subjects were screened for severe cardiovascular, neurological or exercise-limiting joint disorders that would have precluded full participation in the training protocol. Eight subjects were excluded from 79 screened patients: 1 with psychiatric disease, 4 with ischemic heart disease and 3 had exercise-limiting joint disease.

Study II

Seventeen men and women with the diagnosis of moderate to severe COPD participated in the study. COPD individuals with (FEV_1) ≤60% of predicted were included (38). Individuals with acute respiratory exacerbation, with the diagnosis or symptoms of a significant cardiac disease, requiring chronic supplemental oxygen, having resting oxygen saturation <89% measured by pulse oximetry, and who were exercise-limited by orthopedic or joint related diseases were excluded. Twelve healthy age-matched men and women were also involved. All subjects were informed and they signed the written informed consent for their participation. The study was approved by the Institutional Review Board of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

Pulmonary function and exercise test

Each subject performed a series of pulmonary function test (Vmax 229 and Autobox 6200, VIASYS Sensormedics, Yorba Linda, California, USA) including spirometry, body plethysmography and diffusion capacity measurement. COPD patients took 400 μg of salbutamol (in study I) and 400 μg of albuterol (in study II) by inhalation via a spacer 20 minutes before testing in order to maximize bronchodilation. All pulmonary function tests

fulfilled the ATS/ERS guidelines (38). Normal values for spirometry were calculating using the NHANES III standard (38).

An incremental symptom-limited exercise test was performed on an electrically braked cycle ergometer (Ergoline 800, VIASYS SensorMedics) with a pedaling rate of 60 revolutions per minute. After 3 minutes of rest and 3 minutes of loadless pedaling, the work rate was increased by 5-15 watts (W) per minute in a ramp fashion (increment was 5 W/min if FEV_1<1.0 L, 10 W/min if FEV_1 >1.0 L for the COPD patients; increment rate was 15 W/min for the healthy subjects). Pedaling rate was kept constant at approximately 60 rpm. Pulmonary ventilation ($\dot{V}_E$) and gas exchange ((oxygen uptake ($\dot{V}O_2$) and carbon-dioxide output ($\dot{V}CO_2$)) were measured breath-by-breath by a mass flow-sensor and exercise metabolic measurement system (V_{max} Spectra, SensorMedics). The system was calibrated before each test. Lactic acidosis threshold (LAT) was identified by the modified V-slope method (39). Heart rate, 12-lead ECG (Cardiosoft, GE Electric/SensorMedics) and oxygen saturation by pulse oximetry (Radical 7, Masimo) was monitored. Blood gas analysis was done from capillary blood taken from a hyperemic earlobe at rest and peak exercise (AVL Omni7, Ramsey, Minnesota) in study I. Maximal voluntary ventilation was estimated as 40xFEV_1 (40). Shortness of breath and leg fatigue was assessed by the Borg category ratio scale every two minutes during exercise (41). Isotime response, defined as response at the time the shorter of the pre- and post-training incremental exercise test ended, was calculated for several physiological variables.

Study design for Study I

Patients were divided into three groups: C, supervised continuous, n=22; I, supervised interval, n=17; and S, home-based and self-paced, n=32 (Table 1). Patients who lived in the vicinity of the training center and could attend outpatient training sessions were randomized (without stratification) to C or I; those unable to attend supervised training due to unreasonable travel distances were assigned to self-paced training. C and I groups performed exercise training 3 times/week for 45 minutes during an 8-week period. Group C exercise intensity was 80% of peak work rate achieved in an incremental exercise test. Interval training involved a 30 min period of cycling for 2 minutes at 90% followed by 1 minute at 50% peak work rate. This 30 min period was preceded and followed by approximately 7.5 min of exercise at 50% peak work rate (warm-up and cool-down phase). The S group was

instructed to cycle, climb stairs and walk in their natural environment with the same weekly periodicity and time interval as used in in-center programs for 8 weeks. Some patients (10/32) were called monthly and were asked about their condition and training regimen. Subjects in S completed logs reporting date and duration of training sessions.

Activity scale for Study I

Activity was assessed by a questionnaire previously used in this laboratory (42), which includes questions evaluating difficulty in walking, climbing stairs, dressing, cleaning, shopping, housekeeping, working and hobbies. Daily activity was scored on a 0-3 scale (0-not limited, 1-moderately limited, 2-severely limited, 3-not able to do) for 8 items before and after training with a total score of 0 to 24 (≤5: good activity, 5-8: moderately reduced activity, 8-16: severely reduced activity, >16: homebound).

Data collection for Study II

A 16-bit A/D converter digitized (WinDaq Acquisition Version 2.68, Dataq Instruments, Akron, Ohio, USA) at 100 Hz the analog flow signal from the exercise system, and then it was stored on a personal computer for futher analysis. The flow signal was integrated to volume and the volume was calibrated subsequently. The system calibration was succesful for linearity and to have zero intercept; that is why a scalar multiplicative calibration factor was used to adjust the computed expired volume from the flow signal.

Breath-cycle detection for Study II

Because flow towards the end of expiration often fluctuates around zero, it was unsatisfactory to apply a "crossing zero flow" criterion to distinguish the start and the end of a breath cycle. To overcome this, we moved the trigger-threshold to a small negative flow (-0.15 L/s). The start of expiration was defined as the point at which flow exceeded this threshold and remained in a clear positive trend in the next 140 ms. Similarly, the start of inspiration was defined, as the point at which flow achieved this negative threshold, and was followed by clear negative trend in the next 140 ms. After the computerized analysis, each

data set was visually inspected for accuracy and validity of breathing phase change and if necessary it was manually corrected, as a validation procedure for breath cycle detection.

Computing the tidal volume during spontaneous respiration for Study II

Tidal volume calculation was defined by resetting the volume integration with the Riemann Sums method at the start of each expiration (43). The resetting integration compensated for predictable inequalities in inspiratory and expiratory integrated volumes when the respiratory quotient differs from unity.

Computing the rectangular area ratio (RAR) for Study II

Spontaneous expiratory flow-volume curves were analyzed breath-by-breath, and a geometric quantification was performed by custom-made Sigma Plot 10.0 transform functions (SPSS Science, Chicago, IL). The geometric analysis was based on the changes in the shape of the descending phase of the expiratory limb of the SEFV curves. The geometric analysis was defined as an identification of the intra-breath coordinates of two critical anchoring points: ***(A)*** the maximum spontaneous expiratory flow ($\dot{V}_{max}$) and ***(B)*** the point at which the expiratory flow takes a sharp decline signaling the beginning of inspiration ($\dot{V}_{EE}$, 'end-expiratory flow') **(Fig. 4)**. $\dot{V}_{EE}$ was defined as the point associated with the greatest difference between the slopes of adjacent 20 ms segments of the flow-volume curve during the last 0.25 seconds of expiration. These two points were used to make a rectangle from which the breath-by-breath rectangular area ratio (RAR) in the following way was calculated as a measure of concavity defined:

$$RAR = \frac{\int_{V@\dot{V}\max}^{V@\dot{V}EE} \dot{V}\, dV - (\dot{V}_{EE} * V_T)}{V_T(\dot{V}_{\max} - \dot{V}_{EE})},$$

where $V_{@\,\dot{V}\max}$ and $V_{@\,\dot{V}EE}$ are the volumes at $\dot{V}_{\max}$ and $\dot{V}_{EE}$, respectively and V_T is tidal volume. Values of RAR below 0.5 define concavity while values above 0.5 show convexity.

This quantification makes comparisons of curvatures between different loops possible (Fig. 4).

All computer algorithms were developed for breath detection and for the breath-by-breath determination of the parameters of the geometric analysis (RAR, $\dot{V}_{max}$, $\dot{V}_{EE}$ and the relative position of $\dot{V}_{max}$) using SigmaPlot transform functions (SPSS Science, Chicago, IL, USA). We calculated the 30-second bin average values.

Statistical analysis

The results are presented as mean±SD in the text and tables and plotted as mean±SEM in the figures, unless signaled otherwise. Group means were analized by unpaired two-tailed Student's t-tests. To compare means between groups before and after rehabilitation (study I) or at different levels of exercise (study II), we used two-way repeated measures ANOVA with Holm-Sidak *post hoc* analysis of variance to define any individual significance. The statistical analyses were performed in SigmaStat 3.5 (SPSS Science). Statistical significance was accepted at $P<0.05$. Distribution around the mean was expressed ±SD, except in figures, where ±SE was used. Distributions were tested for normality by Kolmogorov-Smirnov test and significance was accepted if $P<0.05$. We targeted in study I the study sample size based on discerning differences in the change in peak oxygen uptake in the incremental test among groups as the primary outcome. We used ANOVA statistics for the 3 groups and asserted that the minimum clinically important difference (44) between groups was 0.1 L/min, the expected standard deviation of change in peak oxygen uptake among subjects was 0.1 L/min, and utilized a power of 0.8 and $\alpha=0.05$. This analysis indicated that 20 subjects in each group would be required.

Results

Study I

In the supervised groups, 31 of 39 subjects were trained 3 times/week (total 24 sessions) (Figure 1). Five of 22 continuous training patients performed fewer sessions than the target, averaging 20 sessions (Figure 1). In the interval group 3 of 17 patients performed fewer sessions than the target, also averaging 20 sessions (Figure 1). Training work rate of supervised continuous training was 74±28W (80% peak work rate). In the interval group work rate fluctuated between 79±25W (90% peak work rate) and 44±14W (50% peak work rate). Therefore over the course of a session, the average work rate was 80% of peak work rate in the C group and 77% in the I group. The actual mean work in the two groups were 161.6±50.6 kJ and 199.8±74.8 kJ in the I and C groups, respectively. The activity logs in self-paced groups revealed average daily training duration was 30±6 minutes and average sessions/week was 3.5±0.2**.** All subjects completed the training protocol. There were no adverse events according to the study protocol.

There were no significant differences in demographics for study participants among the three groups (Table 1). Lung function showed moderate obstruction and hyperinflation at baseline without significant differences among groups. There were no significant changes after training (Table 2).

Percent predicted peak work rate (45) was 67%, 67%, 68% in C, I and S groups, respectively, before training. Peak $\dot{V}_E$ and $\dot{V}_E$/MVV ratio before training did not differ significantly among groups (Table 3), suggesting similar ventilatory limitation. Further supporting this, peak exercise Borg dyspnea scores did not differ among groups. Peak work rate increased significantly in C and I in response to exercise training, but not in S (Figure 2) with increases in C and I groups (12±9 and 14±12W, respectively, $p<0.05$ for each) that were greater than in S (3 ± 12W, NS). A similar tendency was detectable in peak $\dot{V}O_2$, increased significantly in C and I groups, but not in S; however, differences among groups were not statistically significant (Figure 2). LAT increased significantly in supervised groups, averaging 0.08±0.10 and 0.10±0.15L/min in C and I, but not in S (0.04±0.21L/min), while these differences did not achieve the statistical significance. Peak $\dot{V}_E$, heart rate, blood gases, oxygen saturation (SpO_2) and Borg dyspnea, and leg effort scores did not change

significantly as a result of training in any group, showing that exercise led to similar physiologic limitations.

Isotime responses are presented in Table 3 and Figure 3. There were significant reductions in isotime ventilatory equivalent for CO_2 ($\dot{V}_E / \dot{V}CO_2$) and respiratory rate (f) and non-significant reduction tendencies in isotime $\dot{V}_E$ and heart rate (HR) in the supervised constant intensity group (by an average of 3 units, 3 breaths/min, 2 Liter/min and 9 beats/min, respectively). In contrast, in isotime changes in the I and S groups were small, and did not achieve statistical significance.

The activity questionnaire showed reduced activity (average score: 11) at baseline in all groups. After training, there was a significant improvement (i.e., decrease) in activity score in each group (C: 11.5±0.7 vs. 9.0±2.8, I: 10.4±2.4 vs. 7.2±2.1, S: 11.6±2.3 vs. 7.0±1.9; in C, I and S groups; each $p<0.01$ before vs. after training) but differences in improvement among groups did not achieve a statistical significance.

Study II

Subject characteristics and exercise tolerance

The demographic and resting spirometric values of the study population are presented in Table 4. The obstruction was moderate to severe showed by resting pulmonary function in the COPD patients. There were no statistically significant differences in age, height, and weight between the healthy and COPD groups in study II.

COPD patients had a severely impaired exercise tolerance with marked ventilatory limitation as characterized by high end-exercise minute ventilation ($\dot{V}_{E_{peak}}$) to MVV ratio ($\dot{V}_{E_{peak}}$/MVV; 95±21% vs. 54±8% in the COPD patients vs. healthy individuals, respectively; $P<0.05$) whilst healthy individuals suffered from no such difficulties (Table 5).

Breath detection

Each data set was visually inspected for accuracy and validity of breathing phase change and if necessary it was manually corrected, as a validation procedure for breath cycle detection. We count the number of false positive and false negative detections, and calculate the sensitivity for detecting the start of expirations and inspirations. Among the 29 performed test, the false positive detection rate for inspiration and expiration was 1.2±1.1% and

1.9±1.3%, respectively. The false negative rate was 4.2±4.4% for inspirations and 5.0±4.5% for expirations. The data analysis was calculated after manual correction of all these errors in breath detection.

Progressive change in the shape of the spontaneous flow-volume curve during exercise

Figure 4 shows the expiratory loop of the flow-volume curve in a typical healthy individual (upper row) and in a COPD patient (lower row) at rest and at 25%, 75%, and 100% of peak work rate. The shape of the expiratory limb of the SEFV curve at rest and during exercise in the healthy individual, which is reflected by an RAR ≥0.5 (Fig.4, upper row). But in the COPD patient, the expiratory limb of the SEFV curve becomes *concave* at 75% peak work rate (RAR=0.4) and shows more concavity at peak exercise (RAR=0.34) (Fig.4, lower row). Note that both the normal individual and the COPD patient increase intrabreath $\dot{V}_{max}$ and $\dot{V}_{EE}$ with progression of exercise, and that the position of $\dot{V}_{max}$ stays in the middle segment of the tidal volume in the healthy subject even at peak exercise, while within the first quarter of expiration in the COPD patient from early stages of exercise.

Figure 5 illustrates the breath-by-breath analysis of the RAR, $\dot{V}_{\max}$ and $\dot{V}_{EE}$ during the time course of unloaded cycling and incremental exercise in a healthy individual (upper panel) and a COPD patient (lower panel). Superimposed on these plots are smoothed curves calculated by a negative exponential smoothing method (46). The RAR smoothed curve of a healthy individual was above the 0.5 line (in the upper panel of Figure 5) at rest and throughout the exercise, reflecting the convexity of the SEFV curve during the whole test. In the lower panel of Figure 5 it is shown that during unloaded cycling and early into the ramp exercise the RAR smoothed curve in the COPD patient was at or above the 0.5 line, reflecting the convex shape of the expiratory limb of the SEFV curve. At about 5 minutes before peak exercise, the RAR smooth curve fell below 0.5, showing that the SEFV curve became concave. The RAR finally reached a nadir of 0.37 at peak exercise in this COPD patient. It can be seen in this figure, at the time when the RAR smoothed curve fell below 0.5, $\dot{V}_{\max}$ reached about 1.5 L/sec and $\dot{V}_{EE}$ was appreciably above the resting level.

Figure 6 shows the mean RAR plotted as a function of $V_{E\,max}$/MVV at rest and during exercise: at 6, 4, and 2 minutes before end-exercise and at end-exercise, in both healthy and COPD individuals. In healthy individuals (empty circles), RAR at 6 minutes before end-

exercise dropped below the RAR at rest but then progressively increased during the rest of the test; RAR remained significantly above 0.5 in the whole duration of exercise. In marked contrast, average RAR of COPD patients at rest was slightly higher than 0.5 but showed a continuous fall throughout the exercise (average peak exercise value 0.46±0.06). On average, the COPD patients achieved more than 90% of their respiratory reserve (i.e. they are ventilatory limited) at peak exercise (Figure 6).

The number of COPD patients who showed average RAR during the last 30 seconds before exercise end of <0.5 was analysed. Fourteen of seventeen COPD patients manifested averaged RAR<0.5 at end exercise, while in two of the 14 patients the nadir value was only slightly below 0.5 (approximately 0.49). We try to find responsible factors for the failure to develop substantial concavity in these five COPD patients. These patients have a wider range of disease severity (i.e. FEV_1% predicted of 33, 34, 45, 52 and 56); hence, resting lung function does not seem to be a principal determination factor of concavity in the SEFV curve during exercise. Two of the five subjects presented ventilatory limitation (peak V_E/MVV%=103 and 109) and three had substantial ventilatory reserve (mean V_E/MVV%=70±8) at peak exercise. Despite to the other 12 COPD patients who developed definite concavity during exercise, these five patients indicated less dyspnea (Borg dyspnea score: 4.8±1.5 vs. 5.5±1.9) and more leg fatigue (Borg leg score: 5.8±1.6 vs. 4.8±2.0) at peak exercise, while these differences did not reach a statistical significance. All healthy individuals generated RAR smoothed curve remained above 0.5 during the whole exercise.

Discussion

Investigating strategies to improve exercise tolerance in COPD, we compared three rehabilitative training strategies in study I and defined their effectiveness in increasing peak exercise tolerance and in different physiological training variables. The effect of two types of supervised training modalities, like continuous and interval training; were compared to a self-paced, home-based program. Peak work rate in an incremental exercise test showed significant imporvement in the supervised groups, with little difference between C and I groups. Both supervised groups exhibited similar significant increases in $\dot{V}O_{2peak}$ and LAT. Self-paced training yielded only small and insignificant improvements in these measures. Analysis of variance revealed that the difference in increase in peak work rate, but not $\dot{V}O_{2peak}$ and LAT between the supervised groups, and the self-paced groups achieved statistical significance.

Related to exercise intolerance in study II we have shown that our novel, computerized method allows characterization of the genesis and development of progressive expiratory flow limitation that occurs during exercise in COPD patients in a non-invasive and unobtrusive way. To the best of our knowledge, this is the first approach on a breath-by-breath basis that allows quantification of EFL by characterizing the profile of the SEFV curve. Our method does not require additional instrumentation beyond the flow sensor and digitizing equipment for the analog output of the flow sensor, in opposite of NEP measurement and the forced oscillation technique. The algorithm for this analysis might be implemented as a software module, and easily can be used in preexisting computerized cardiopulmonary exercise systems. Furthermore, it does not require invasive maneuvers and provides a fully quantitative, objective and dynamic measurement of developing flow limitation during exercise on a breath-by-breath basis.

Activity becomes progressively reduced by shortness of breath, and it can lead to deconditioning in COPD patients (1, 2). Aerobic enzyme concentrations, mitochondrial density, muscle fiber-to-capillary ratio decrease, and there is reduction of muscle mass and type I fiber fraction in these type of COPD patient (47).

According to previous studies, COPD patients could achieve a physiological training effect; it has now been clearly shown that high intensity endurance training yields increases in $\dot{V}O_{2peak}$ (3) and the ability to sustain a given work rate (3). Training can result in an increase in the muscle capillary-to-fiber ratio leading to a reduction in capillary to mitochondria diffusion distance (48) and increasing oxidative enzyme content and myoglobin levels (48), which was detected by muscle biopsy.

Optimal strategies to increase exercise tolerance through rehabilitative exercise were sought. A key finding was that high intensity training achieved greater physiologic effect than low intensity training (3). Recent studies have focused on strategies allowing COPD patients to exercise at higher training work rates; in randomized double-blind trials oxygen administration (49,50) and bronchodilator therapy (51) have been shown to increase rehabilitative exercise training effectiveness (52).

Home-based exercise programs have been found effective in increasing exercise tolerance and quality of life (5), but the relative effectiveness compared to supervised programs can be questionable. Home-based programs have discernable disadvantages. Frequent encouragement and instruction by trained rehabilitation personnel can be crucial adjunct to rehabilitation. Ongoing interaction with patients similarly afflicted is posited to assist in motivating patients to comply with rehabilitative therapy. It has clinical importance to compare effectiveness of home-based programs with supervised group programs; previously only two studies have been reported in this field (6, 7).

COPD patients have been compared in a 12-week program with twice-weekly sessions of either home-based (15 patients) or in-center exercise (15 patients) by Strijbos et al. (7). Equal improvements in exercise capacity and reduction in breathlessness and leg fatigue have been found at the program's end and 3 months later in the two groups. However, some benefits (exercise capacity and Borg dyspnea score) persisted to a greater extent in the home-based program after 18 months. It has been an important study feature that therapists visited the home for each exercise session; this is not practical in many settings and is not a general set-up of most home-based programs that have been reported. Puente-Maestu et al. have compared responses of 41 COPD patients to 8 weeks of in-center rehabilitation 4 times/week vs. a home-based program with weekly in-center visits to maintain adherence (6). Estimated mean training work rate has definitely been higher in the in-center rehabilitation group and exercise tolerance measures (exercise duration, $\dot{V}O_{2peak}$, heart rate, isotime $\dot{V}_E$,

$\dot{V}CO_2$ and lactate accumulation) have also shown greater improvement in the in-center program.

In our study, the self-paced program employed was more similar to that of Puente-Maestu et al. (6) than to that of Strijbos et al. (7) in that in home rehabilitation there were no personnel visits. Like Puente-Maestu, we found only small non-significant trends in physiological training measures. While home-based training may indicate of improvement the patient's perception of activity level (as indicated by our activity questionnaire), it seems inferior to supervised training in improving exercise endurance. Only small, non-significant improvement in peak exercise capacity, ventilatory, cardiovascular and metabolic responses was detected; improvement in peak exercise tolerance was significantly less than in the supervised groups. We suspect that supervised training in a supportive environment in the presence of others similarly afflicted results in superior training results.

Training intensity is determined by the effectivity of interval training as well as its effectiveness in inducing training effects in the exercising muscles. Traditionally, it has been shown that below "critical training intensity" there is no achieved training effect, no matter how long the training proceeds (53). Above this threshold, progressively higher intensities achieve progressively greater training effects, and exercise training can reduce dynamic hyperinflation of COPD patients (54), although it is not certain that this relationship is linear. If, for example, continuous training intensity performed at the critical training intensity is compared with interval training where intensity fluctuates below and substantially above the critical intensity, it is reasonable to expect that interval training will be more effective. Alternately, if continuous training set at a work rate above the critical training intensity, and it is compared to interval training with work rate fluctuating around this mean but always remaining above the critical intensity, it is difficult to predict which will be more effective (possibility the continuous training will be more effective than the interval training). It is difficult to predict which regimen will be better tolerated in the sense that the total tolerable work may be greater with one or the other strategy.

Coppoolse et al. have studied 21 COPD patients randomized to a continuous or interval training profile with the same total work per session performing an 8-week 5-session/week, 30-minute/session exercise program (4). Exercise testing has demonstrated

that, for most response measures, physiologic changes have been more marked in the continuous training group.

Vogiatzis et al. have studied 36 COPD patients who performed in endurance training with 40-minute sessions held twice weekly. Subjects have been randomized into two groups, a constant work rate group (50% of peak work rate) or an interval group (30 seconds at 100% of peak work rate alternating with 30 seconds of rest) (8). Physiologic benefits have been detected in both groups with no clinically important difference.

Puhan et al. (55) has recently found no significant difference in the improvement of exercise capacity and quality of life of COPD patients performing interval or constant work rate training. However, the work intensities set in this study have been somewhat lower than the ones used in previous studies (4, 8) or in the present study: training work rate in the constant work rate group was only 57% of peak work rate achieved in an incremental test, and the total work per session of those performing interval training was only 76% of that performed by the constant work rate training group. In addition, the duration of the training sessions was only 20 minutes in either group.

In the present study both supervised training groups had high intensity work rate profiles. The continuous training group exercised at 80% peak work rate in an incremental exercise test. This is similar to the strategy employed previously (3) and is a near-maximal target (56). Interval training changed to a substantial fraction of the time (2/3) to be spent at an even higher training intensity: 90% peak work rate, and another 1/3 spent at lower intensity (50% peak work rate) phase. The average exercise intensity was therefore 77% of peak work rate and similar to that of the continuous work rate group. Interval and continuous work rate profiles yielded similar physiologic response changes, and therefore, similar training effects as it can be seen in in Figure 1 and 2.

An additional information was that in both supervised groups, exercise intensity was held constant during the training program in order to make a strict comparison between the two strategies. It differs from the most previous reports of exercise training in COPD, in which training intensity has been increased as tolerated during the intervention. Substantially higher training work rates can be set in the latter strategy as the program proceeds (e.g., patients are able to exercise for the entire session at work rates approximating the peak in pre-training incremental exercise testing) (56). It can be a reason why training-induced increases

in the supervised groups in, for example, $\dot{V}O_{2peak}$ are somewhat less in our study compared to some other COPD training studies (4, 57).

Previous analyses compared to our new *quantitative* method have been mainly limited by the shape of spontaneous flow-volume curve to qualitative inspection. A non-sinusoidal expiratory flow pattern was characteristic of obstruction, and pointed out that as EFL progresses the $\dot{V}_{max}$ is reached earlier in the tidal breath reported by Morris and Lane (58). Spontaneous flow-volume profiles of anaesthetized patients has been monitored by Bardoczky and d'Hollander, pointing out the "bowing configuration" in the expiratory limb as an indication of diffuse obstruction (59). Previous analysis found relation between the flow limitation and the presence of concavity of the expiratory limb of the flow-volume loops (60). Baydur and Milic-Emili could detect the flow-volume shape in association with the NEP method qualitatively (60) and SEFV curve concavity in patients with a high percentage of tidal volume exhibiting flow-limitation monitored according to NEP; two-thirds of the patients with SEFV curve concavity have been reported with >50% of tidal volume exhibiting flow-limitation, and half of the patients showing concavity had >70% of tidal volume exhibiting flow limitation.

In our study, 14 of 17 COPD patients performed a value of RAR <0.5 before peak exercise. Althought, five subjects with low FEV_1 did not show substantial concavity in their SEFV curve. None of the normal subjects had the RAR smoothed curve drop below 0.5 at any point of exercise. Comparing an age-matched control group, we demonstrated the real difference considering the possibility that the normally occurring decrease in elastic recoil with ageing might be associated with these configuration changes.

There is, however, a wide range of subjects who achieved 'minimal' RAR at peak exercise in the COPD group, and it is worthwhile to consider possible mechanisms of concavity that might lead to this variability. Several factors might be crucial to lead to concavity of the SEFV curve. Rapid drop in expiratory flow rate can cause concavity in the flow-volume loop demonstrating dynamic airway compression (23,29,33). Rapid and shallow breathing adopted by COPD patients augments the drop in expiratory flow rate, which is at a frequency that limits effective ventilation to lung compartments with short time constants. Our data support the observation of Morris et al. (58), that as $\dot{V}_{max}$ rises during exercise, there is a shift of the position of the $\dot{V}_{max}$ to move in earlier position in the expired volume. High

intrathoracic pressures achieved during expiration might lead to gas compression and a result of dynamic airway compression (24). Futhermore, gas compression might occur in the presence of expiratory flow limitation (24, 28). An increasing role of active expiration in moderate to severe COPD patients and the configurational changes might also be consistent. Further studies are warranted to determine the relative contribution of these potential mechanisms.

One of the critical development tasks for this analysis was the "breath cycle determination" algorithm. Using a slightly negative threshold is valuable to eliminate the influence of noisy flow signal toward the end of expiration. Post-detection visual inspection of approximately 14,000 flow-volume loops demonstrated that using a slightly negative flow threshold to detect the beginning and end of expiration we achieved a low false positive and false negative rate in determining both inspirations and expirations. This finding suggests that in subsequent studies, visual confirmation of accuracy of breath detection by this algorithm will not be needed.

Accurate determination of the anchoring points ($\dot{V}_{max}$ and $\dot{V}_{EE}$) has a potential limitation of RAR measurement technique because of noise in the expiratory flow signal. Breath-by-breath physiologic changes in the exhalation can be other possible reasons for the variability in RAR, which results inaccuracy of concavity or convexity of the expiratory limb of SEFV curve. Furthermore, we observed that the configuration of SEFV curve sometimes varies considerably between subsequent breaths that might lead to errors in determining the critical anchoring points for the calculation of RAR. Interestingly, the breath-to-breath variability was generally greater in healthy subjects than in COPD patients. We suppose that part of this variability might come from random changes in compliance or vibrations within the airways that is less characteristic in COPD. Additionally, the SEFV curve adopts more convex configuration in healthy subjects (58), from which it is more difficult to separate the intrabreath peak- and end-expiratory flow, leading to variability in RAR calculations. In order to minimize the effect of breath-by-breath variability, we smoothed the breath-by-breath data using a single component exponential smoothing method (61) which allowed characterization of trends. Another way of diminishing the effect of breath-to-breath configuration changes of the SEFV curve would be to average several consecutive breaths and calculate the RAR based on the averaged curves. A third way of dealing with this variability would be to exclude from further analysis RAR values that were outliers from the general trend. These methods might be explored in future studies.

In summary, the training study supports the concept that in-center high intensity supervised rehabilitation programs can be more effective as shown by physiologic evidence of improved exercise tolerance than home-based unsupervised programs, while some of the measured physiologic variables did not achieve statistical significance. We could not demonstrate difference in effectiveness of interval training as compared with constant work rate training with similar total work per session. The interval training might have a greater training effect presumably because of the higher muscle tension during the exercise periods. In future studies other interval work rate strategies might be found, which might be more effective. In theory interval training has less load for the pulmonary vasculature (especially important in pulmonary hypertension), and patients can tolerate more easally this training modality (62).

According to exercise intolerance, flow limitation, the quantification of concavity of the expiratory limb of the SEFV curve by means of calculation of the RAR breath-by-breath seems to be a valuable method for assessing development of EFL in COPD patients. The shape change of the loops develops as a consquence of progressively active expiration and dynamic airway compression. Hence, the measurement of RAR seems to have clinical importance in routine assessment of progressive flow limitation in COPD and may show a factor to critical ventilatory limitation and dyspnea. Further studies are needed to compare the results of this breath-by-breath quantification with other methods of EFL determination such as the NEP method and the forced oscillation technique. Further research is also needed to explore the validity and reliability of this method in stratification of COPD patients across the total range of disease severity. There might be an association between dynamic hyperinflation measurement and the observed SEFV configuration changes.

Acknowledgements

The training study was supported by funds available to the Department of Pulmonology, Szeged University, Deszk, Hungary.

I would like to express my thanks first and foremost to Professor Attila Somfay MD, PhD, for initiating my scientific career, for providing me with the opportunity to carry out my scientific work and for his invaluable scientific guidance and help.

I am very grateful to Professor Richard Casaburi PhD, MD and Dr. Janos Porszasz MD, PhD for inviting and allowing me to perform clinical research in exercise physiology in their laboratory at Harbor-UCLA, Los Angeles; their helpful comments and constructive criticism were always of enormous help and were greatly appreciated.

This work was supported by scholarship, many thanks for the support to the President and Advisory Board of the Hungarian Pulmonological Foundation.

I wish to express my gratitude to my parents for their love, patience, trust and support.

All colleagues, director and staff members at the Department of Pulmonology, University of Szeged, Deszk, Hungary and at the Rehabilitation Clinical Trials Center, Harbor-UCLA Medical Center, Torrance, Los Angeles, USA are gratefully thanked for creating such a supportive and pleasant working environment.

I am indebted to Dr. Krisztina Boda MS, PhD, who helped me to analize and find valuable statistical method to interpret our results.

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Tables

Table 1. Demographic characteristics of Study I participants

	Supervised continuous (C) group (n=22)	Supervised interval (I) group (n=17)	Self-paced (S) group (n=32)
Age (year)	61 ± 12	67 ± 10	60 ± 12
Height (cm)	167 ± 7	166 ± 7	168 ± 6
Body weight (kg)	73 ± 12	67 ±10	71 ± 12
BMI (kg/m^2)	26 ± 4	25 ± 4	25 ± 4
Male:Female	19:3	11:6	25:7

Mean±SD; BMI: body mass index

Table 2. Resting lung function and blood gases before and after rehabilitation in Study I

	Supervised continuous (C) group (n=22)		Supervised interval (I) group (n=17)		Self-paced (S) group (n=32)	
Lung function	Before training	After training	Before training	After training	Before training	After training
FEV_1 (liter)	1.5 ± 0.5	1.5 ± 0.5	1.7 ± 0.7	1.8 ± 0.7	1.5 ± 0.5	1.5 ± 0.5
FEV_1 (%pred)	51 ± 16	52 ± 17	64 ± 29	66 ± 23	52 ± 16	52 ± 17
FVC (liter)	2.9 0.8	3.0 ± 0.8	3.0 ± 0.7	3.1 ± 0.8	3.0 ± 0.7	3.0 ± 0.7
FVC (%pred)	82 ± 17	82 ± 15	90 ± 23	93 ± 22	84 ± 17	86 ± 19
FEV_1/FVC (%)	50 ± 12	49 ± 12	57 ± 17	57 ± 16	50 ± 13	49 ± 12
TLC (%pred)	110 ± 16	110 ± 17	116 ± 13	111 ± 21	119 ± 16	117 ± 21
FRC (%pred)	136 ± 33	139 ± 34	147 ± 33	140 ± 39	157 ± 30	153 ± 40
RV (%pred)	164 ± 48	160 ± 42	171 ± 53	149 ± 46	179 ± 44	176 ± 52
RV/TLC (%)	54 ± 10	52 ± 10	54 ± 13	48 ± 7	56 ± 11	55 ± 10
D_LCO (%pred)	67 ± 17	69 ± 20	67 ± 26	65 ± 13	62 ± 26	63 ± 21
PaO_{2rest} (mmHg)	65 ± 8	64 ± 6	67 ± 7	73 ± 15	66 ± 7	65 ± 7
$PaCO_{2rest}$ (mmHg)	43 ± 4	42 ± 4	42 ± 7	39 ± 5	42 ± 5	43 ± 6

Mean±SD; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; D_LCO: diffusion capacity of carbon monoxide; PaO_2: arterial partial O_2 pressure; $PaCO_2$: arterial partial CO_2 pressure.

Table 3. Exercise testing results before and after rehabilitation in Study I

		Supervised continuous (C) group		Supervised Interval (I) group		Self-paced (S) group	
		Before training	After training	Before training	After training	Before training	After training
Peak	$\dot{V}O_2$ (Liter/min)	1.17±0.40	1.27±0.40*	1.10±0.31	1.18±0.36*	1.12±0.37	1.17±0.35
	$\dot{V}_E$ (Liter/min)	51 ± 17	51 ± 16	46 ± 11	49 ± 14	48 ± 12	47 ± 11
	f (breath/min)	45 ± 7	41 ± 7*	44 ± 6	42 ± 7	44 ± 6	41 ± 7*
	HR (beat/min)	138 ± 26	133 ± 22	130 ± 17	129 ± 36	139 ± 24	138 ± 22
	SpO_2 (%)	93 ± 2	94 ± 2	92 ± 6	94 ± 2	92 ± 2	92 ± 4
	$\dot{V}_E / \dot{V}CO_2$	40 ± 5	37 ± 4	39 ± 5	38 ± 4	43 ± 10	41 ± 7
	$\dot{V}_E$ /MVV (%)	90 ± 24	89 ± 22	68 ± 29	76 ± 24	85 ± 19	83 ± 22
	PaO_2 (mmHg)	71 ± 10	70 ± 10	67 ± 7	70 ± 10	68 ± 8	68 ± 8
	$PaCO_2$ (mmHg)	43 ± 6	44 ± 7	42 ± 7	42 ± 5	44 ± 5	43 ± 6
	Borg (dyspnoea)	6.4 ± 2.5	5.7 ± 2.7	6.6 ± 2.2	6.0 ± 2.1	7.4 ± 1.8	6.7 ± 2.5
	Borg (leg fatigue)	6.2 ± 2.9	5.9 ± 3.1	6.9 ± 2.2	6.1 ± 2.5	6.6 ± 2.3	6.3 ± 2.6
LAT	$\dot{V}O_2$ (Liter/min)	0.82±0.22	0.92±0.24*	0.83±0.29	0.96±0.28*	0.84±0.25	0.91±0.25
	$\dot{V}_E$ (Liter/min)	32 ± 7	36 ± 7	32 ± 8	35 ± 9	33 ± 7	36 ± 7
	f (breath/min)	27 ± 5	27 ± 6	29 ± 6	30 ± 5	26 ± 4	27 ± 4
	HR (beat/min)	119 ± 23	111 ± 23	110 ± 19	114 ± 18	120 ± 20	121 ± 19
	SpO_2 (%)	93 ± 2	94 ± 2	94 ± 2	93 ± 6	93 ± 2	93 ± 4
	$\dot{V}_E / \dot{V}CO_2$	41 ± 6	38 ± 11	41 ± 5	40 ± 6	43 ± 10	43 ± 8
Isotime	$\dot{V}O_2$ (Liter/min)	1.14±0.37	1.15±0.35	1.07±0.26	1.06±0.34	1.10±0.35	1.11±0.33
	$\dot{V}_E$ (Liter/min)	48 ± 16	46 ± 16	42 ± 10	42 ± 14	45 ± 10	44 ± 10
	f (breath/min)	33 ± 6	30 ± 6*	33 ± 7	31 ± 7	31 ± 6	31 ± 7
	HR (beat/min)	139 ± 24	130 ± 19	127 ± 17	125 ± 20	136 ± 23	133 ± 21
	SpO_2 (%)	93 ± 3	93 ± 3	93 ± 3	92 ± 5	92 ± 3	92 ± 4
	$\dot{V}_E / \dot{V}CO_2$	41 ± 6	38 ± 5*	38 ± 7	41 ± 8	41 ± 8	41 ± 7

Mean±SD, *p<0.05; $\dot{V}O_2$: oxygen uptake; $\dot{V}_E$: minute ventilation; f: breathing rate; HR: heart rate; SpO_2: oxygen saturation; $\dot{V}_E / \dot{V}CO_2$: ventilatory equivalent; MVV= FEV_1x40: maximal voluntary ventilation; LAT: lactate anaerobic threshold.

Table 4. Demographic and pulmonary function characteristics of Study II subjects

	Healthy (n=12)	COPD (n=17)
Age (years)	60± 9	63±10
Height (cm)	169±9	169±10
Weight (kg)	74±15	77±12
FEV_1 (L)	3.1±0.8	1.1±0.5*
FEV_1 %pred.	104±13	39±12*
FVC (L)	4.0±1.0	2.8±1.1*
FVC %pred.	103±14	77±20*
FEV_1/FVC%	77±4	40±7*
MVV (L)	123.5±31.1	43.7±18.9*
PEF (L/s)	7.6±1.9	3.3±0.9*
TLC (L)	6.3±1.3	7.1±2.1
TLC %Pred.	108±12.9	113±17.8
FRC (L)	3.2±0.7	4.8±1.5*
FRC %Pred.	104±23.1	146±29.4*
RV (L)	2.3±0.5	3.8±1.4*
RV %Pred.	107±16.8	163±46.8*

Mean±SD, * P<0.05; %pred values in pulmonary function were calculated according to NHANES III standard[38]. FEV_1: forced expiratory volume in the 1st second; FVC: forced vital capacity; MVV: maximum voluntary ventilation (FEV_1 X 40)[40]; PEF: peak expiratory flow; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume.

Table 5. Exercise tolerance and end-exercise ventilatory characterization (Mean ± SD) in Study II.

	Healthy (n=12)	COPD (n=17)
Peak WR (Watts)	145±38	68±35*
$\dot{V}O_{2peak}$ (L/min)	1.75±0.49	1.14±0.37*
$\dot{V}_{E\ peak}$ (L/min)	66±19	40±14*
$\dot{V}_{E\ peak}$/MVV (%)	54±8	95±21*
V_T (L) at end-exercise	2.1±0.54	1.2±0.38*
RAR at end-exercise	0.61±0.05	0.46±0.06*

Mean±SD; * P<0.05; Peak WR: peak work rate in the incremental test; $\dot{V}O_{2peak}$: peak oxygen uptake at end exercise; $\dot{V}_{E\ peak}$: peak minute ventilation; $\dot{V}_E$ /MVV : ratio of peak minute ventilation and maximal voluntary ventilation ($MVV=FEV_1*40$) [40]; RAR: rectangular area ratio; V_T: tidal volume.

Figure legends for Study I

Figure 1: Flow of participants through each study stage.

Figure 2: Change in peak oxygen uptake ($\dot{V}O_2$), the lactic acidosis threshold (LAT) and peak work rate as a result of training in the three training groups.

*p<0.05 vs. self-paced training, errors bars represent ±SE

Figure 3: Change in isotime responses as a result of training during an incremental exercise test in the three training groups. $\dot{V}_E$, minute ventilation; f, respiratory rate; HR, heart rate; $\dot{V}_E / \dot{V}CO_2$, ventilatory equivalent for carbon dioxide.

*:p<0.05 vs. supervised continuous training, #:p<0.05 vs. self-paced training, error bars represents ±SE.

Figure 1.

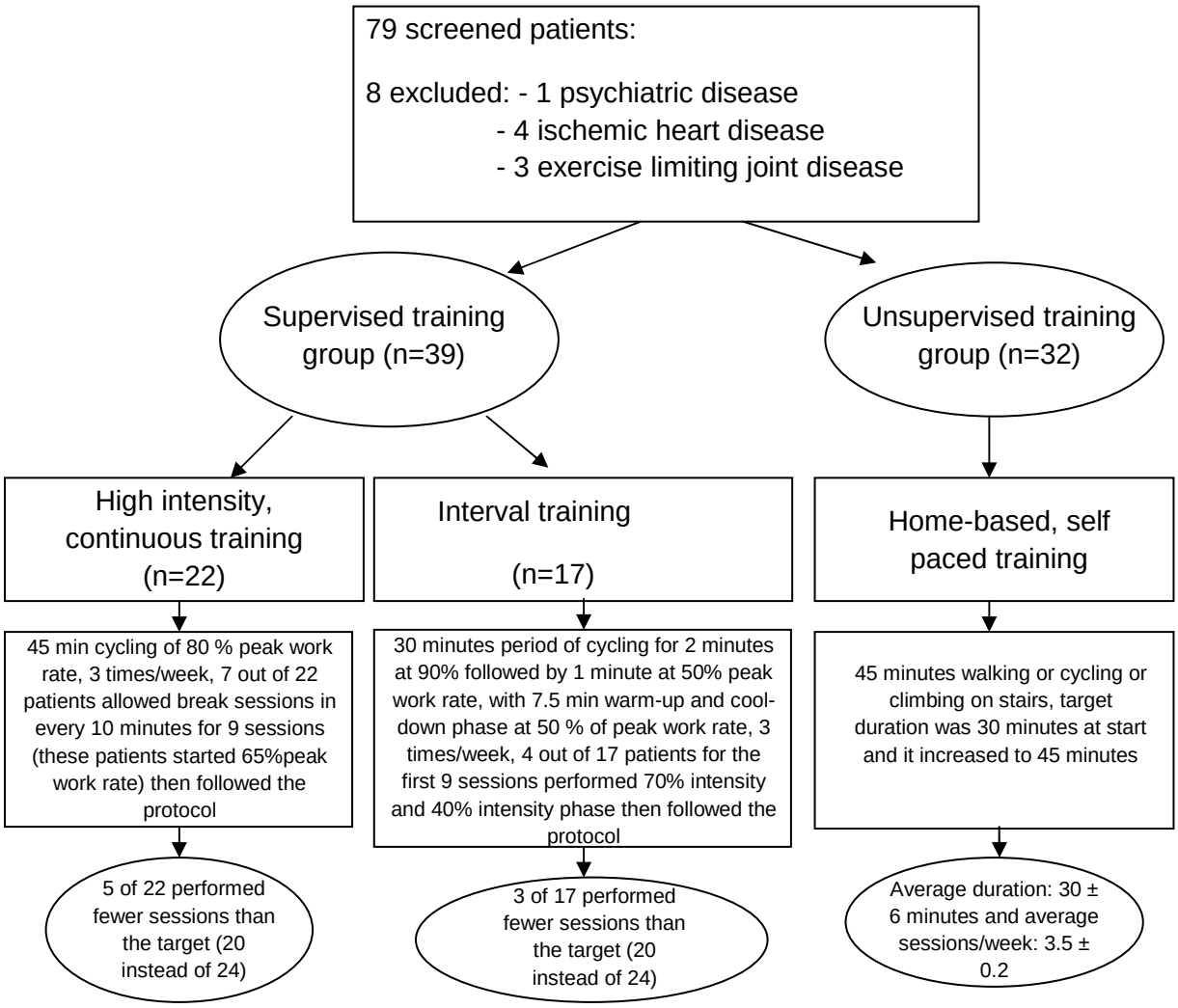

79 screened patients:
8 excluded: - 1 psychiatric disease
- 4 ischemic heart disease
- 3 exercise limiting joint disease
Supervised training group (n=39)
Unsupervised training group (n=32)
High intensity, continuous training (n=22)
Interval training (n=17)
Home-based, self paced training
45 min cycling of 80 % peak work rate, 3 times/week, 7 out of 22 patients allowed break sessions in every 10 minutes for 9 sessions (these patients started 65%peak work rate) then followed the protocol
30 minutes period of cycling for 2 minutes at 90% followed by 1 minute at 50% peak work rate, with 7.5 min warm-up and cool-down phase at 50 % of peak work rate, 3 times/week, 4 out of 17 patients for the first 9 sessions performed 70% intensity and 40% intensity phase then followed the protocol
45 minutes walking or cycling or climbing on stairs, target duration was 30 minutes at start and it increased to 45 minutes
5 of 22 performed fewer sessions than the target (20 instead of 24)
3 of 17 performed fewer sessions than the target (20 instead of 24)
Average duration: 30 ± 6 minutes and average sessions/week: 3.5 ± 0.2

Figure 2.

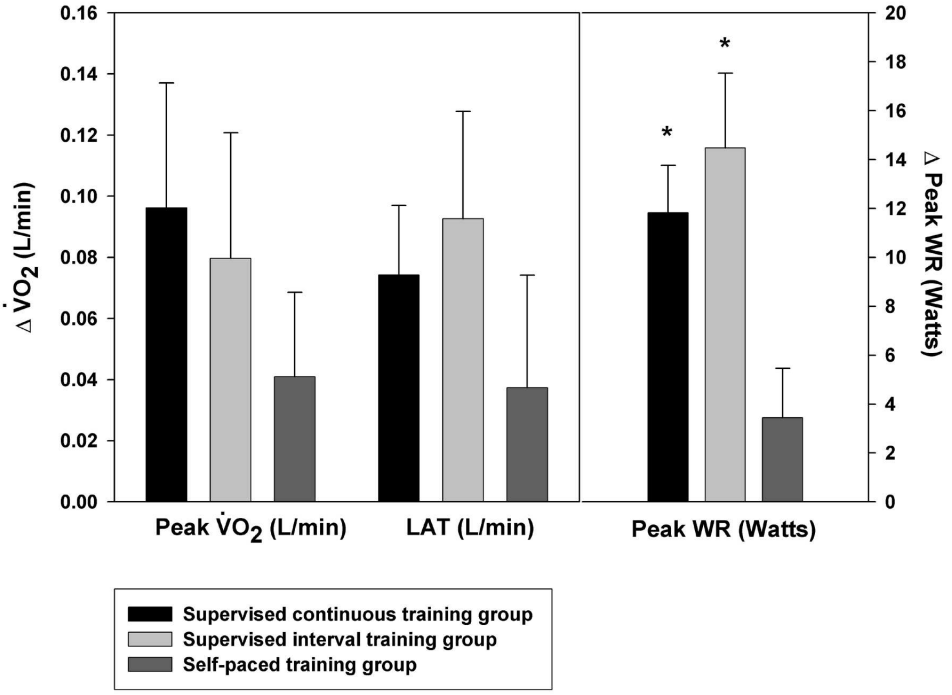

0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Δ V̇O2 (L/min)
20
18
16
14
12
10
8
6
4
2
0
Δ Peak WR (Watts)
*
*
Peak V̇O2 (L/min)
LAT (L/min)
Peak WR (Watts)
Supervised continuous training group
Supervised interval training group
Self-paced training group

Figure 3.

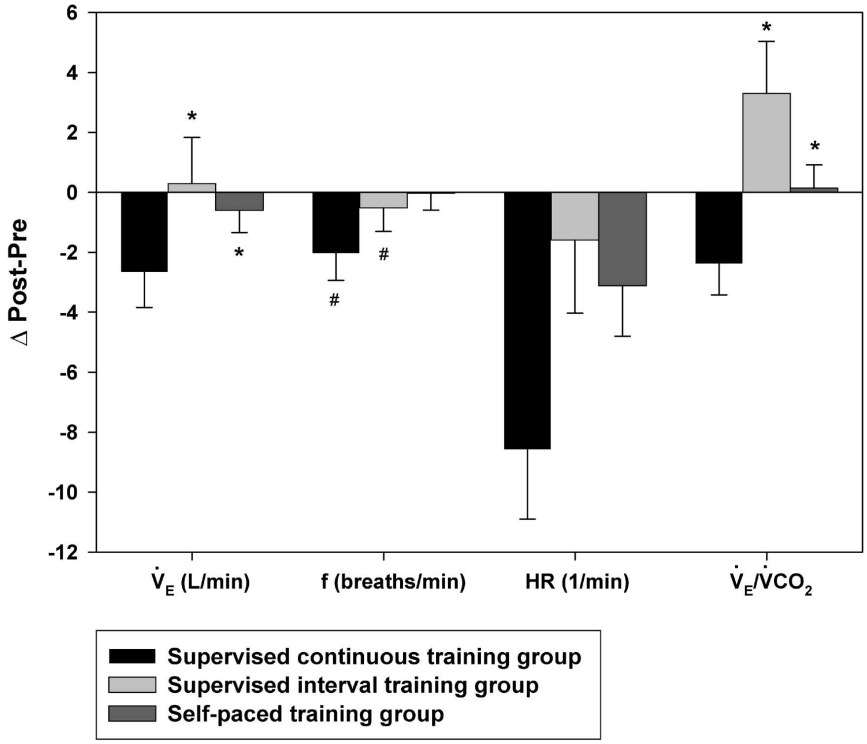

6
4
2
0
-2
-4
-6
-8
-10
-12
Δ Post-Pre
*
*
*
#
#
*
*
V̇E (L/min)
f (breaths/min)
HR (1/min)
V̇E/V̇CO2
Supervised continuous training group
Supervised interval training group
Self-paced training group

Figure legends for Study II:

Figure 4. Progression of the spontaneous flow-volume (SEFV) curve configuration during incremental exercise. Top row: a healthy individual (FEV_1=3.7 L, 81% predicted). Bottom row: a severe COPD patient (FEV_1=1.0 L, 29% predicted). The shaded portion is the area used to calculate the rectangular area ratio (RAR); the triangle bounded by the dotted line, using the peak expiratory flow ($\dot{V}_{max}$) and the end expiratory flow ($\dot{V}_{EE}$) as anchor points, represents a RAR of 0.5, demonstrating no curvature. The healthy individual has a RAR that remains above 0.5, indicating SEFV curves with consistently convex profiles at all exercise levels. The COPD patient displays a declining RAR that achieves a minimum of 0.34 at peak exercise, indicating a markedly concave SEFV curve configuration as exercise progresses. Note that both the normal individual and the COPD patient increase intrabreath $\dot{V}_{max}$ and $\dot{V}_{EE}$ with progression of exercise and that the position of $\dot{V}_{max}$ stays in the middle segment of the tidal volume in the healthy subject, while remaining within the first quarter of expiration in the COPD patient. PWR: peak work rate, WR: work rate, V_E: minute ventilation, MVV: maximal voluntary ventilation calculated as FEV_1*40.

Figure 5. Breath by breath time course (open circles) of rectangular area ratio (RAR), peak expiratory flow ($\dot{V}_{max}$) and end-expiratory flow ($\dot{V}_{EE}$) during an incremental exercise test. The boldface lines represent smoothed data (exponential method [61]). Note that the ordinate scales for $\dot{V}_{max}$ and $\dot{V}_{EE}$ are different in order to better represent the changes. Panel A: a healthy person (51 yrs, female, FEV_1: 2.72 L (98% predicted)). Panel B: a COPD patient (66 yrs, male, FEV_1: 1.02 L (29% predicted)).

Figure 6. Rectangular area ratio (RAR) responses occurring at rest and as exercise limitation is approached during incremental exercise in healthy individuals (n=12, open circles) and COPD patients (n=17, closed circles). The abscissa presents mean V_E/MVV at rest and at 6, 4, 2 and 0 minutes prior to end-exercise from left to right, respectively. RAR values of COPD patients are lower at rest and at all phases of exercise as compared to normal, non-obstructed subjects (repeated measures ANOVA $P<0.01$). The RAR is significantly less than at rest starting 4 minutes before end-exercise (repeated measures ANOVA $P<0.01$). In normal subjects, RAR is significantly higher than at rest starting two minutes prior to end of exercise (repeated measures ANOVA $P<0.01$). The index of ventilatory limitation (V_E/MVV x 100) approaches a value of 100% in the COPD patients but not in the healthy individuals.

Figure 4

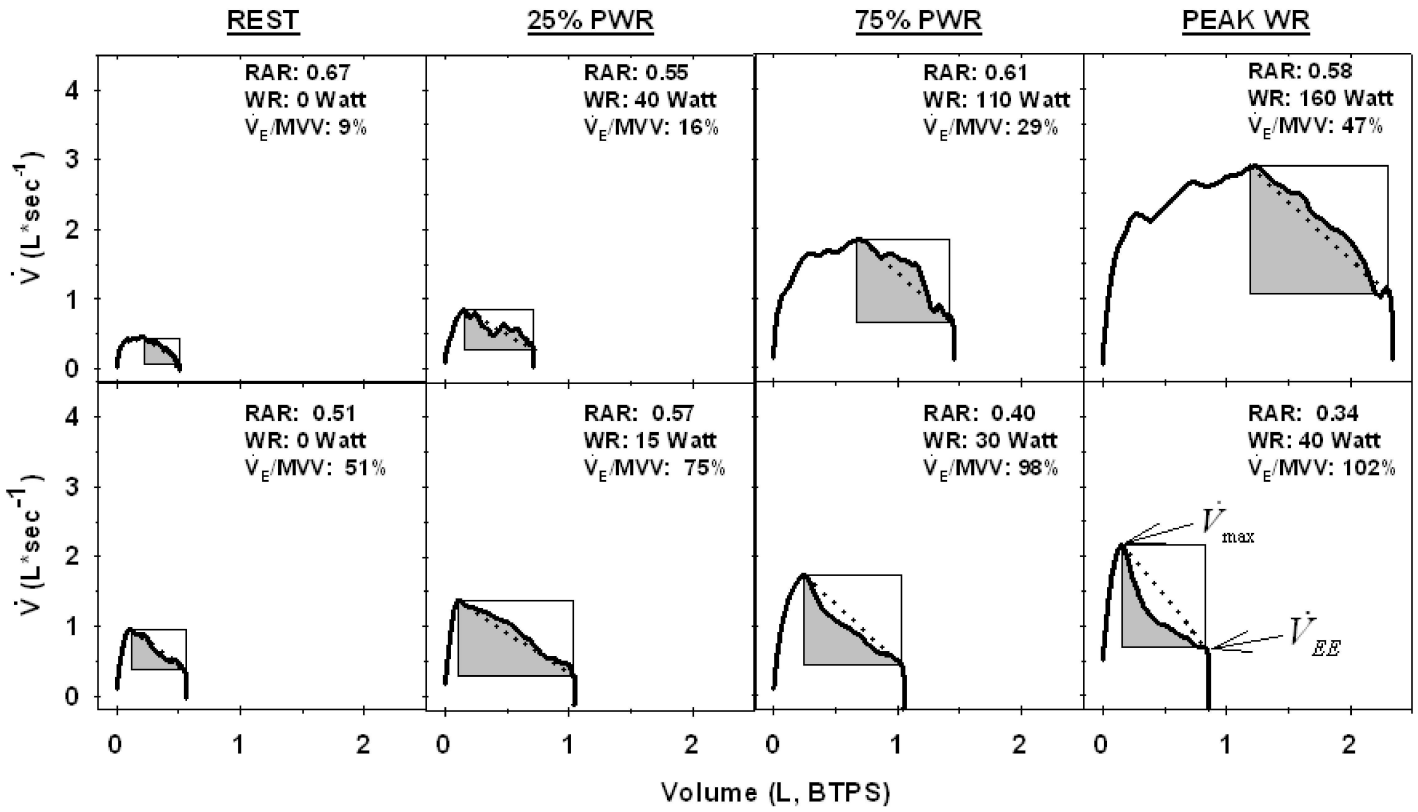

REST
25% PWR
75% PWR
PEAK WR
RAR: 0.67
WR: 0 Watt
V̇E/MVV: 9%
RAR: 0.55
WR: 40 Watt
V̇E/MVV: 16%
RAR: 0.61
WR: 110 Watt
V̇E/MVV: 29%
RAR: 0.58
WR: 160 Watt
V̇E/MVV: 47%
RAR: 0.51
WR: 0 Watt
V̇E/MVV: 51%
RAR: 0.57
WR: 15 Watt
V̇E/MVV: 75%
RAR: 0.40
WR: 30 Watt
V̇E/MVV: 98%
RAR: 0.34
WR: 40 Watt
V̇E/MVV: 102%
V̇ (L*sec-1)
V̇max
V̇EE
Volume (L, BTPS)

Figure 5/A

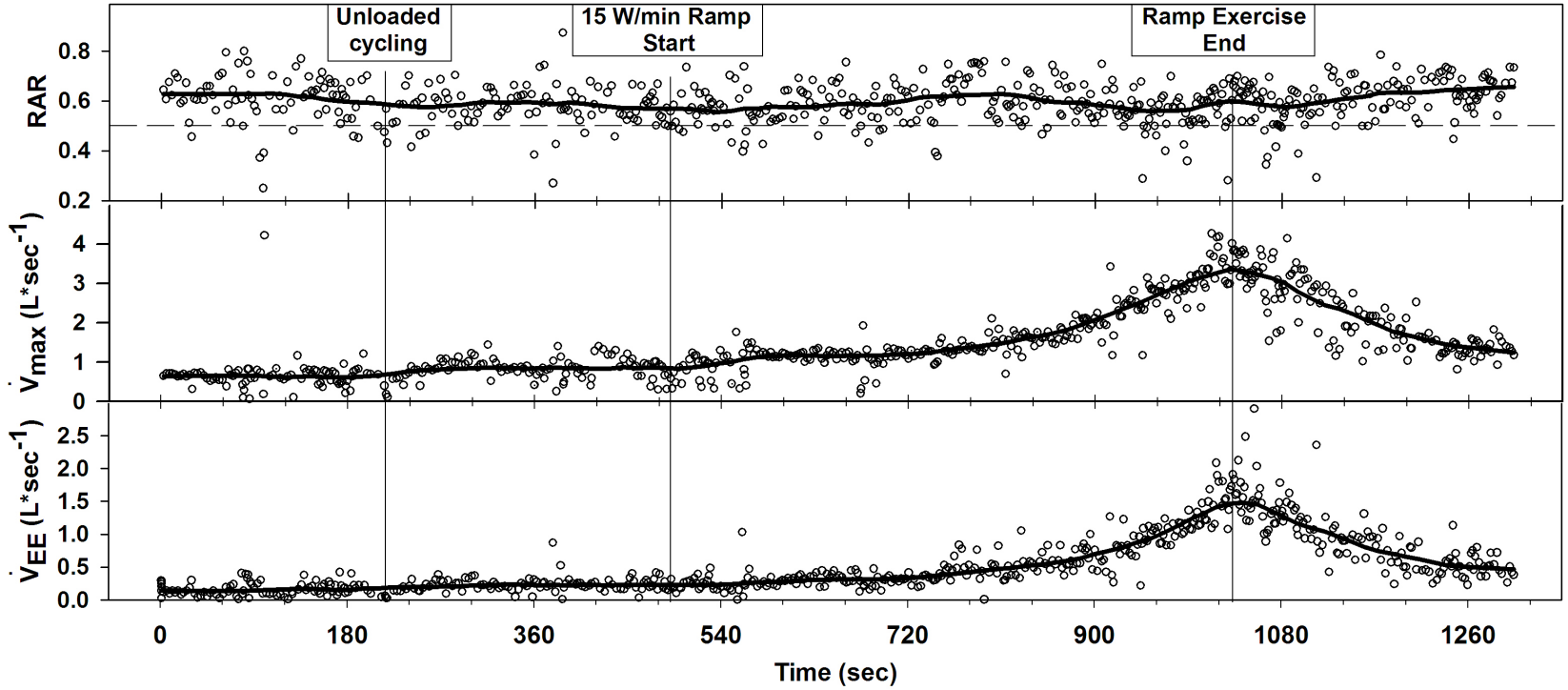

Unloaded cycling
15 W/min Ramp Start
Ramp Exercise End
RAR
0.8
0.6
0.4
0.2
$\dot{V}_{max}$ (L*sec^{-1})
4
3
2
1
0
$\dot{V}_{EE}$ (L*sec^{-1})
2.5
2.0
1.5
1.0
0.5
0.0
0
180
360
540
720
900
1080
1260
Time (sec)

Figure 5/B

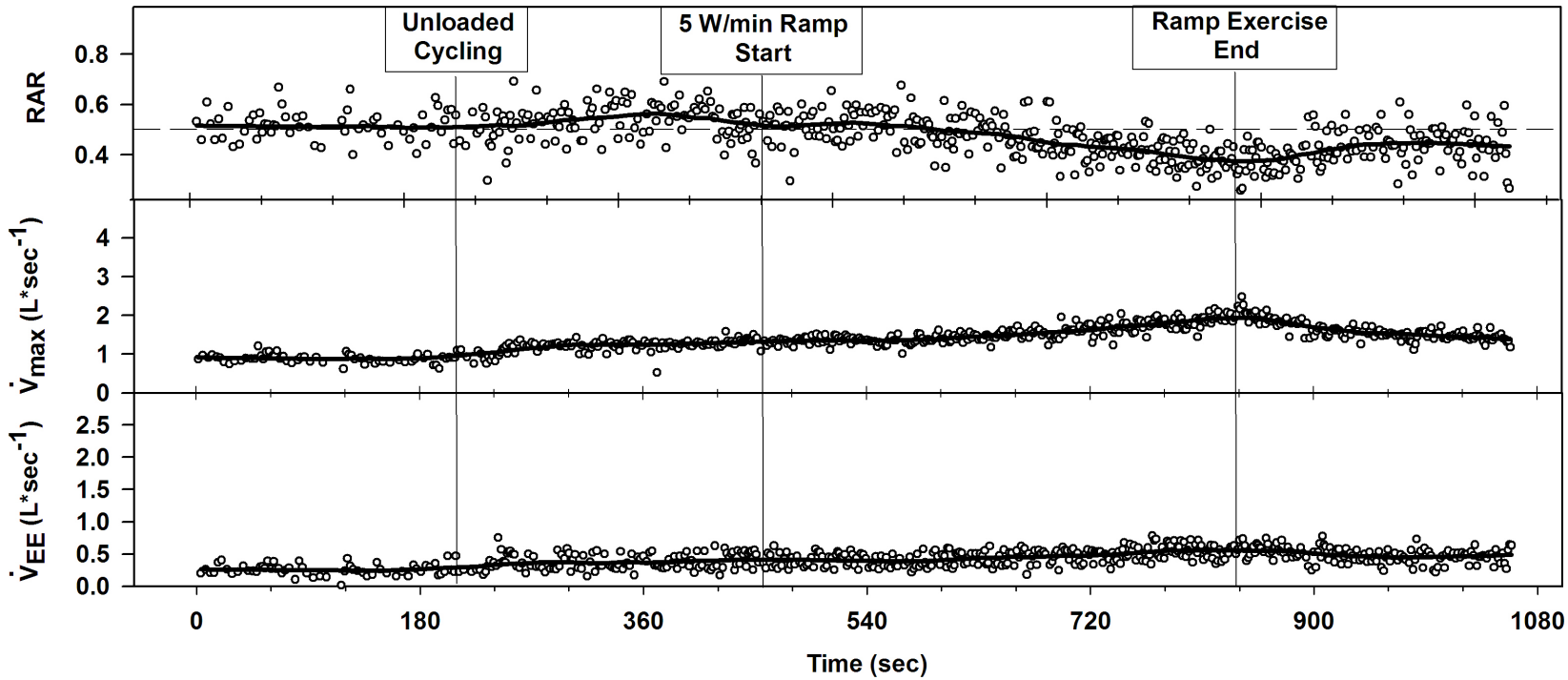
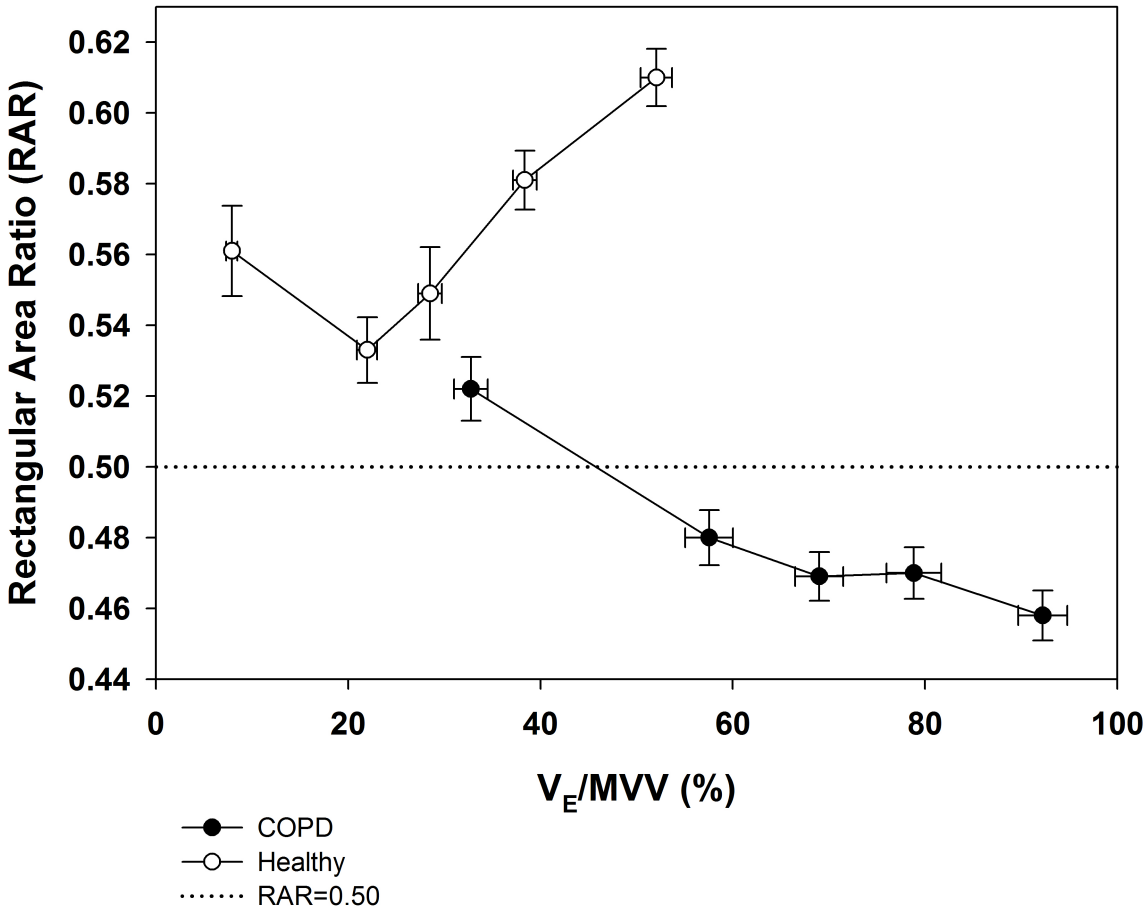

Unloaded Cycling
5 W/min Ramp Start
Ramp Exercise End
RAR
0.8
0.6
0.4
$\dot{V}_{max}$ (L*sec^{-1})
4
3
2
1
0
$\dot{V}_{EE}$ (L*sec^{-1})
2.5
2.0
1.5
1.0
0.5
0.0
0
180
360
540
720
900
1080
Time (sec)

Figure 6


Rectangular Area Ratio (RAR)
0.62
0.60
0.58
0.56
0.54
0.52
0.50
0.48
0.46
0.44
0
20
40
60
80
100
V_E/MVV (%)
COPD
Healthy
RAR=0.50