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CARDIOPULMONARY STRESS DURING EXERCISE TRAINING IN PATIENTS WITH COPD

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Running Head: Cardiopulmonary stress and exercise in COPD

Abstract

Background: exercise training is an essential component of pulmonary rehabilitation. However, the cardiopulmonary stress imposed during different modalities of exercise training is not known yet. We measured the cardiopulmonary stress of a 12-week exercise training program in 11 COPD patients (FEV_1 42±12%pred; age 69±6yrs). **Methods:** pulmonary gas exchange and heart rate of 3 training sessions were measured with a portable metabolic system at the beginning, midterm and end of the program. Symptoms were assessed with Borg Scores. The exercise intensity was compared to the recommendations for exercise training by the American College of Sports Medicine (ACSM). **Results:** training effects were significant (ΔW_{max} 14±11 Watts, 6MWT 44±36 meters; $p<0.05$ for all). Whole body exercises (cycling, walking and stair climbing) consistently resulted in higher cardiopulmonary stress ($V'O_2$, $V'E$ and HR) than arm cranking and resistance training ($p<0.05$). Dyspnea was higher during cycling than resistance training ($p<0.05$). Patients exercised more than 70% (>20 minutes) of the total exercise time above 40% of the $V'O_2$ reserve and HR reserve ("moderate" intensity according to the ACSM) throughout the program. **Conclusions:** Exercise training based on guidelines using a fixed percentage of baseline peak performance and symptom scores achieves and sustains training intensities recommended according to the ACSM. In addition, the applied training program resulted in relatively homogeneous $V'O_2$ responses, while HR response is much more variable. This would not incite for the use of HR to guide training intensity in COPD. The cardiopulmonary stress during

resistance training is lower than during whole body exercise and results in less symptoms.

Introduction

Pulmonary rehabilitation programs (PR) have consistently improved exercise capacity, symptoms and quality of life of patients with chronic obstructive pulmonary disease (COPD). Exercise training is an essential component of PR[1] and endurance training is commonly used. Generally, the endurance type of training applied during PR includes cycling and/or treadmill walking. Programs including relatively high-intensity endurance training have proven to be effective[1]. However, in addition to walking and cycling, other exercise modalities have been described during PR for COPD patients, *e.g.,* resistance training[2], callisthenics[3], arm cranking[4] and stair climbing[5]. In clinical rehabilitation, a combination of several of these exercises, is often applied. Although it is known that high intensity training leads to more desirable physiological training effects than low intensity training[6], the cardiopulmonary stress imposed by different exercises are not known yet. In addition, training intensity is conventionally set at a given fraction of an incremental peak exercise response. Due to the relatively slow oxygen uptake kinetics of patients with chronic diseases[7;8] the actual metabolic load during somewhat longer exercise bouts may well be underestimated.

To improve cardiorespiratory fitness, the guidelines for exercise testing and prescription of the American College of Sports Medicine recommend, for healthy individuals, to exercise 3 to 5 times a week, at 40-85% of the maximum oxygen uptake or heart rate reserve for more than 20 minutes continuously or in intervals[9]. Whether these recommendations are achieved by patients with COPD is debated[1]. It is unknown whether the exercise training regimens applied in the context of PR programs are sufficient to exercise COPD patients at recommended intensities for healthy individuals. Moreover, the amount of time patients train at given intensities has not been studied yet.

Therefore, we measured the cardiopulmonary stress of the different components of an exercise training program in the context of pulmonary rehabilitation in patients with moderate to severe COPD. In addition, we also analysed if patients were able to exercise at intensities recommended by the American College of Sports Medicine.

Materials and methods

Study subjects

Eleven consecutive patients visiting the outpatient clinic entered the study. The following criteria were used for patient selection: (1) clinical diagnosis of COPD; (2) stable condition at inclusion with no recent infection or exacerbation; (3) remaining symptoms of dyspnea and reduced exercise capacity despite optimal medical treatment; (4) no locomotor or neurological condition or disability limiting the ability to exercise; (5) no need of supplemental oxygen at rest nor during exercise due to the inability of the equipment to measure $V'O_2$ while breathing inspiratory O_2 fractions higher than 21%; (6) patients had to be able to attend the outpatient rehabilitation center three times per week. Patients who met the inclusion criteria gave oral informed consent to take part in the study. They performed testing at inclusion and after 3 months of outpatient pulmonary rehabilitation. All tests were part of the routine screening of COPD patients who enter a rehabilitation program approved by the Medical Ethical Board of the University Hospitals Leuven. The tests consist of measurement of pulmonary function, peripheral and respiratory muscle strength, exercise capacity, and quality of life. Details of all the performed tests have been described before[4].

Maximal Exercise Capacity

Maximal exercise capacity was assessed by maximal cycle ergometry. The test was performed on a magnetically-braked cycle ergometer (Ergoline 900, Bitz, Germany) according to the standards of the ATS/ACCP statement on

Cardiopulmonary Exercise Testing[10]. After three minutes of unloaded pedalling, patients cycled at an incremental work rate (+10W/min) until exhaustion. Heart rate (HR) was monitored continuously by a 12 lead electrocardiogram. Ventilation (*V'*E), oxygen uptake ($V'O_2$), and carbon dioxide production ($V'CO_2$) were measured throughout the test. $V'O_{2max}$ was referred to predicted values[11]. On-line calculations of breath-by-breath *V'*E, $V'O_2$, $V'CO_2$ and respiratory exchange ratio (RER) were obtained with the Vmax*ST* 1.0 (Viasys, MEDA, Belgium), which is a portable metabolic system. The device is secured to the upper chest with a harness and due to its low weight (650g), it has minimal discomfort. The volume measurement is done by a turbine (Triple-V®). $V'O_2$ is analysed with an electro-chemical cell, and $V'CO_2$ is measured by an infrared analyser. A similar model of this device has been validated by Prieur et al.[12]. A face mask with a dead space of <30 mL (Hans Rudolph Inc, Kansas City MO/USA) was carefully adjusted to the patients' face and checked for air leaks.

Training Program

The 12-week training program consisted of 1.5-hour training sessions which patients attended 3 times per week. The circuit training, included cycling, walking, leg press for lower extremity resistance training, arm cranking and stair climbing. The training program is based on previous experience[4] and driven by symptoms' perception by the patient. Training intensity was set at 60% of the initial maximal work rate for ergometry cycling, at 75% of the average walking speed during the 6MWT for treadmill walking and at 70% of the one repetition maximum (1RM) (the maximum load which can be moved only once over the full range of motion without compensatory movements) for leg press resistance training. For walking, the average walking speed was determined dividing the distance walked by the time (6 minutes) during the 6MWT performed at admission in the rehabilitation program. Arm cranking and stair climbing (two-step chair) were performed in 2-minute blocks (1 to 3 sets). Physiotherapists increased patients' work rate or duration on a weekly basis, guided by a schedule and Borg-symptom scores. A Borg score of 4-6 for dyspnea or fatigue was set as a target[13]. Close supervision was provided during training, with a ratio of one physiotherapist for every four patients. In addition to the exercises, patients also followed education sessions regarding disease management and medication use. There was also individual psychological and social counselling and nutritional and occupational therapy.

Exercise training session assessments

By the end of week 1, 6 and 12 of the PR program, patients performed one exercise training session with the Vmax*ST*. On-line breath-by-breath measurement of $V'E$, tidal volume ($V'T$), $V'O_2$, $V'CO_2$, respiratory rate (RR) and the ratio between inspiratory time and total cycle time (Ti/Ttot) were recorded by the Vmax*ST* throughout the training session. HR was assessed by a heart rate monitor (Polar®, T31 Kempele, Finland). All variables were recorded at rest (two minutes baseline) and during the whole exercise training session, which was identical to the previous clinical rehabilitation session. The session was supervised by a different physiotherapist, who was not involved in the clinical management of the patient. The exercises were performed in a fixed order. After two minutes of unloaded cycling as a warming up, patients started the loaded cycling, which was followed by leg press resistance training, treadmill walking, arm cranking and finally stair climbing*.* Sufficient rest was assured after each exercise (patients rested until they felt able to continue). Patients could move freely without discomfort, as the device has a low weight. Pilot data showed that patients were not hindered in their exercise performance by the device[14;15]. The face mask could be removed during the resting periods between exercises, if necessary.

Patients were asked to grade their symptoms of dyspnea and fatigue during the exercises using the Modified Borg Score.

Data handling

Signals from the Vmax*ST* were transmitted during the training session by telemetry to a portable computer for online inspection of data quality. After the test, stored data were downloaded from the Vmax*ST* to ensure complete breath-by-breath datasets and analysed in the software (Metasoft Version 1.9.0, 1998-2001).

In order to label the intensity at which patients were exercising, the recommended exercise intensity according to the Guidelines of the American College of Sports Medicine (ACSM) were applied to the cardiopulmonary data. The ACSM recommends an intensity of exercise corresponding to 40% to 85% of oxygen uptake reserve ($V'O_2R$) or heart rate reserve (HRR) to increase and maintain cardiorespiratory fitness[16]. The $V'O_2R$ is calculated from the difference between resting and maximum $V'O_2$. Similarly, HRR is the difference between resting and maximum HR. The thresholds considered as “moderate” and “hard” by the ACSM were used[16]. This means training intensities above 40% ("moderate") and 60% ("hard") of the $V'O_2R$ and HRR. To estimate the training intensity "moderate" and "hard", 40% and 60% of this value, respectively, is added to the resting $V'O_2$ and/or resting HR and is expressed as a percentage of $V'O_2R$ or HRR. A typical formula reads as follows: $V'O_2R = V'O_{2rest} + 0.6\ (V'O_{2max} – V'O_{2rest})$.

Statistical Analysis

The Statistical Analysis System (SAS Institute, Cary, NC, USA) and the GraphPad Prism 3.0 (GraphPad Software, San Diego, USA) were used for data analysis.

Data were checked for normal distribution with the Kolmogorov-Smirnov test.

The effects of exercise training were analysed with paired t-test. The cardiopulmonary measurements assessed in week 1, 6 and 12 were analysed with the Repeated-measures ANOVA. If p value was lower than 0.05, the Tukey's post test was performed. For the symptom scores, the comparison was done with the Friedman test. In this case, if p value was lower than 0.05, the Dunn's post test was performed[17]. Level of significance for all comparisons was set at $p<0.05$.

Results

The studied group (**Table 1**) showed moderate to severe airflow obstruction and was classified within GOLD stages II (n=4), III (n=4) and IV (n=3). One patient had an acute exacerbation and could not be reassessed in week 6. Another patient withdrew from the rehabilitation program in week 12 for personal reasons and could not perform the final exercise training session with the Vmax*ST*. However, all the other measurements after 12 weeks were successfully performed by this patient. Although the assessments with the VmaxST throughout the exercise training sessions were well tolerated by patients, in week 12 two patients reported difficulties exercising while wearing the equipment (6% of measurements).

Training effect

As expected, FEV_1 remained unaltered after 12 weeks of exercise training ($\Delta FEV_1=0.02\pm0.18$ L; p=0.41). $V'O_{2max}$, W_{max} and 6MWT increased significantly after training (0.09±0.13 L/min, 14±11 Watts and 44±36 meters, respectively; p<0.05 for all). There was no statistically significant difference in isometric quadriceps force (ΔQF=5±16 Nm; p=0.25), despite a significant increase of the training load of the leg press resistance training during the program (Δload=53±30 Kg; p=0.0001, which represents 43±26 % increase). $V'O_2$, $V'CO_2$, $V'E$ and HR at iso-work rate (100% of the initial maximal work rate) decreased significantly after 12 weeks of exercise training (reductions of 7, 15, 9 and 7%, respectively; p<0.02 for all).

Cardiopulmonary response and symptoms during the exercise training program

Figure 1 shows the progression of the training load for cycling, leg press resistance training and walking during the exercise training program. There were patients who sustained high intensity training from the first week on and were able to tolerate further increments in the exercise load during the program. However, others improved their training load less than predicted (**Figure 1**). Participation rate was 97%.

There was no difference in heart rate before starting a given exercise in week 1, 6 and 12 ($p=0.39$, 0.60 and 0.36, respectively).

There was an overall increase in $V'O_2$, $V'E$ and HR during leg press and arm cranking throughout the 12 week program ($p<0.05$ for both). $V'E$ during stair climbing was also higher in week 12 ($p=0.02$). For the remaining exercises, despite significant increase in work rate, $V'O_2$, $V'E$ and HR remained unchanged over time. Symptoms reported during exercises did not change throughout the program, except for an increased dyspnea during arm cranking ($p<0.05$) and an increase in fatigue during walking ($p=0.02$) at the end of the program.

$V'O_2$, $V'E$ and HR responses of a representative patient during a training session in week 1 are illustrated on **Figure 2.** This patient (male, 51 kg, FEV_1 0,88 L) cycled at 55 Watts (69% W_{max}) for ten minutes, performed leg press resistance training (3 sets of 8 repetitions) with 110Kg (70% 1RM), walked on the treadmill with a speed of 4.2 Km/h (74% $6MWT_{speed}$) for ten minutes, and performed arm cranking and stair climbing for two minutes each. The values of $V'O_2$, $V'E$ and HR achieved at the end of the different exercises by this patient were close to maximal values obtained during the initial incremental exercise test.

The average cardiopulmonary stress imposed by the different exercise modalities throughout the training program is shown in **Table 2.** Relatively high intensity exercise in terms of $V'O_2$, $V'E$ and HR was reached from the first week on. The cardiopulmonary responses were lower during arm exercises (arm cranking) and resistance training (leg press) when compared to whole body exercises (cycling, walking and stair climbing) (Table 2). Similarly to $V'O_2$, $V'E$ and HR, symptoms of dyspnea reported by patients were consistently lower during leg press when compared to cycling ($p<0.05$ week 1, 6 and 12). In terms of fatigue sensation, leg press induced less fatigue than cycling at week 12 ($p<0.01$).

The ventilatory equivalent for oxygen ($V'E/V'O_2$) was systematically lower during walking when compared to cycling during the program ($p<0.001$). Note that $V'O_2$ was not different between these two exercises. The respiratory exchange ratio (RER) was also higher during cycling when compared to walking in week 1 and 12 ($p<0.0001$).

Exercise time and thresholds of exercise intensity

The duration of the trainings increased over time and were 66±7, 81±7 and 80±13 minutes in week 1, 6 and 12, respectively (ANOVA, p=0.02). The corresponding exercise time was 30±3 minutes in week 1, 38±4 minutes in week 6 and 36±10 minutes in week 12 (ANOVA, p=0.03). This represents 46, 47 and 45% (week 1, 6 and 12, respectively) of the training session.

Figure 3 shows the total exercise time as well as the time above the thresholds considered "moderate" and "hard" (≥40% and ≥60% of $V'O_2R$ or HRR, respectively) by the ACSM in week 1, 6 and 12. Patients spent more than 80% of the total exercise time above 40% of $V'O_2R$ ("moderate" threshold) (88±7%, 89±7% and 84±9% in week 1, 6 and 12, respectively) (ANOVA, p=0.18). Concerning the HRR, patients achieved "moderate" intensities for more than 70% of the total exercise time (76±29%, 71±22% and 83±23% in week 1, 6 and 12, respectively) (p=0.36) (**Figure 3A**). For the threshold considered "hard" (≥60% of $V'O_2R$ or HRR), patients spent 67±25% of the total exercise time above this intensity in terms of $V'O_2R$ in week 1 and 75±15% in week 6 and 12 (ANOVA, p=0.33). Slightly less time was spent above the intensity "hard" in terms of HRR; 51±42% in week 1, 48±30% in week 6 and 64±34% in week 12) (ANOVA, p=0.26) (**Figure 3B**).

There was poor agreement between the thresholds based on the $V'O_2R$ in comparison to those based on the HRR throughout the program. An example of this lack of concordance between these two thresholds of exercise intensity is shown in **Figure 4.**

Discussion

The present study showed that the applied exercise training program enabled the studied group to achieve and sustain training intensities that are well within the limits of what is proposed to be effective for healthy adults according to the ACSM. In addition, resistance training (leg press) resulted in less cardiopulmonary stress when compared to whole body exercises. Lastly, we showed a poor concordance between intensity based on $V'O_2R$ and heart rate reserve, *i.e.,* an acceptable training intensity in terms of $V'O_2R$ was reached at a heart rate which would be considered too low.

Work rate progression and whole body exercises

Although guidelines were given for work rate progression, this progress was variable among patients due to symptoms (**Figure 1**). The work rate progress patients presented during the training may partially have been the result of an improvement in movement efficiency as we observed relatively larger increase in training load (intensity and duration) than in $V'O_2$. Milani et al.[18] have previously shown that COPD patients improve mechanical efficiency to a larger extent than $V'O_2$ after exercise training.

For most of the patients, the intensity achieved during cycling, walking and stair climbing was high enough to produce oxygen consumption and ventilation close to maximal responses achieved in the baseline incremental cycling. Although the three whole body activities (cycling, walking and stair climbing) resulted in similar cardiopulmonary responses, they have different characteristics and were performed in different ways. During cycling, most of the patients performed interval training (5 to 8 sets of 2-minute blocks). This is a common approach to be able to train at relatively high work rates. Others have shown that COPD patients achieve higher work rates during interval training when compared to continuous training[19]. During treadmill walking, most of the patients tolerated longer blocks of continuous exercise, even with increments in walking speed and duration. This is probably due to the differences between these two exercise modalities. In comparison to cycling, walking has been shown to be less fatiguing and to produce less lactate at similar $V'O_2$ levels[20–22]. Hence, patients may exercise longer. During cycling, more lactate is produced which results in a continuous rise in ventilation (the so-called slow phase of ventilatory rise at iso-load)[21]. In order to cope with the increasing ventilatory stress, the exercise blocks (especially during cycling) were divided into shorter blocks. Although we did not measure lactate in the present study, the higher RER and $V'E/V'O_2$ during cycling compared to walking are suggestive of more lactate production. In addition, other differences during cycling and walking, such as more hypoxemia[22;23] and increased dead space[22] may also have influenced the performance of these exercises.

During stair climbing, patients also stepped in short blocks (1 to 3 sets of 2-minute blocks). This activity resulted in similar levels of $V'O_2$, $V'E$, HR and symptoms, as cycling and walking. The profile of stair climbing is, however, different, as patients reach peak exercise responses very quickly. Therefore, it is difficult, if not impossible, to sustain this activity for longer periods with the current applied pace (around 22 steps/min) and step height (21 cm). The fixed order of the exercises, with stair climbing being the last one, could potentially have led to a gradual increase in the cardiopulmonary stress and may have increased kinetics of the cardiopulmonary adaptation[24]. However, patients were able to rest for long periods before starting a given exercise, which allowed heart rate to decrease sufficiently after each activity. Furthermore, others have shown the high cardiopulmonary stress imposed by stair climbing. Previous studies showed that in patients with chronic airflow obstruction[25] and chronic heart failure[26] stair climbing represents strenuous exercise, eliciting physiologic responses similar to cycle ergometry and treadmill tests.

Arm exercise and Resistance training

The cardiopulmonary stress imposed by arm exercise and resistance training was lower when compared to whole body exercises (cycling, walking, and stair climbing). Carter and co-workers[27] found reduced work capacity for arms compared to legs in COPD patients. This is a consequence of the smaller muscle mass involved during arm exercises. However, although the cardiopulmonary response was lower during arm cranking in comparison to cycling, there was no difference in symptoms of dyspnea. This may be due to the features of the pulmonary disease which may also hinder the performance of arm work, such as dyssynchronous breathing[28], involvement of inspiratory muscles of the rib cage in upper torso and arm positioning[29], nutritional status[30] and dynamic hyperinflation[31].

For leg press resistance training, in addition to the lower cardiopulmonary stress, patients also experienced less dyspnea in comparison to cycling. Richardson et al. showed that exercising the quadriceps muscle alone (knee extensor exercise) resulted in lower peak values of $V'O_2$, $V'E$ and HR and less symptoms of dyspnea when compared to cycling[32]. In addition, the lower cardiopulmonary stress achieved during leg press can also be attributed to the average duration of this exercise. The exercise time for leg press was 2 minutes throughout the training (3 sets of 8 repetitions), what may also have contributed to the lower cardiopulmonary response The reduced sensation of dyspnea during leg press is not surprising, since during resistance training, patients are not usually limited by the central cardiorespiratory limitations commonly present in COPD. This will result in less symptoms, and consequently, patients are able to achieve significantly higher relative work rates[32;33]. Although patients presented an increase in load during quadriceps resistance training, this progression was lower than what was anticipated based on experience in healthy elderly[34;35]. However, the load progression observed in the present study was similar to what was achieved in other studies including COPD patients which showed a significant effect on lower limb muscle force[2;5].

Exercise time and thresholds of exercise intensity

In the present study, patients spent less than half of the total time of the training session executing the prescribed exercises. This was due to the characteristics of most of the exercises performed (intermittent) and the relatively long periods of rest patients needed in order to recover after each exercise. Intermittent exercise has been shown to be time consuming[36]. In addition, Lacasse et al.[37] showed that COPD patients have a lower heart rate recovery after exercise when compared to healthy subjects, requiring longer rest periods.

There was a higher variability in exercise time in week 12. This variability was mainly added to the data since two patients could not perform the exercises as planned due to complaints such as dyspnea on the day of the assessment. The thresholds of exercise intensity achieved in this study are those proposed by the ACSM to improve cardiorespiratory fitness. Exercises should be performed 3 to 5 times a week at the intensity within 40-85% of the $V'O_2R$ or HRR for more than 20 (or at lower intensity preferably 30) minutes continuously or in intervals[9]. In the present study, patients succeeded in achieving these thresholds, as they exercised 3 times a week at more than 40% of the $V'O_2R$ (which corresponded to 55% of baseline $V'O_{2max}$) and HRR (corresponding to 84% of baseline HR_{max}) for more than 20 minutes (considered as "moderate" intensity by the ACSM). When higher intensities were set (≥60% of the $V'O_2R$ and HRR; ACSM's "hard" intensity), we observed that the time patients were exercising at such intensities was lower. However, patients still remained more than 20 minutes above the threshold "hard" concerning $V'O_2R$ (corresponding to 70% of baseline $V'O_{2max}$). In terms of HRR, patients only exercised at ≥60% of the HRR (which corresponded to 89% of baseline HR_{max}) for more than 20 minutes in week 12. In the present study, training intensities target following published guidelines and symptoms resulted in a homogeneous response of thresholds based on $V'O_2$. Much more variable, however, was the response based on HR. The poor agreement between time spent above the thresholds based on $V'O_2$ and HR may be related to different factors. The differences between the HR and $V'O_2$ kinetics might be one of them. It has been shown in COPD that HR kinetics is slower when compared to the $V'O_2$ kinetics during exercise[8]. In addition, ventilatory limitation to exercise is often present in patients with COPD. Consequently, it is common that patients stop exercising before reaching their cardiocirculatory limits[38]. These features indicate that heart rate may not be an appropriate target to set exercise intensity to COPD patients. This has been previously suggested by others[39].

Limitations of the study

Patients who needed oxygen supplementation could not be included in the study. This was due to the inability of the Vmax*ST* equipment to measure $V'O_2$ while breathing inspiratory O_2 fractions above 21% (room air). Therefore, the present results may not be readily extrapolated to the more severe patients. However, since leg press resistance training elicited less $V'E$ and dyspnea than whole body exercise in the present study, we may expect that the more severe patients may especially benefit from this type of exercise. These patients usually have dynamic hyperinflation[31] and ventilatory limitations are more apparent, hence, small muscle group training may be especially interesting in this population.

The present study does not allow to identify the minimal training intensity at which COPD patients should exercise in order to achieve physiological training effects. We rather investigated the cardiopulmonary stress imposed during clinical rehabilitation at a given fraction of the peak work rate.

The small sample size could be considered a limitation since it may hinder the generalization of the results. Specifically, we did not include severe oxygen-dependent COPD patients in our study. In addition, although the exercise training applied to the COPD patients is rather similar among centres, there might be differences in the programmes which may result in different cardiopulmonary stress. Nevertheless, our data strongly support the relatively high cardiopulmonary stress of whole body exercise training in COPD.

In summary, the results of the present study provide new insight into training intensity imposed to COPD patients with conventional exercise training programs, since the majority of the patients trained at relatively high work rates. Without knowing the results of the metabolic assessments during the training, physiotherapists were able to keep patients at high intensity training based on guidelines using a fixed percentage of baseline peak performance further guided by symptoms scores. The patients with moderate to severe airflow obstruction included in the study tolerated relatively high intensity training and obtained significant improvements in exercise capacity after completion of the program. The cardiopulmonary stress during resistance training is, as expected, lower than during whole body exercise and results in less symptoms. The applied exercise training program enabled the studied group to achieve and sustain training intensities that are recommended according to the American College of Sports Medicine. Exercise training based on guidelines using a fixed percentage of baseline peak performance and symptom scores seems to result in relatively homogeneous $V'O_2$ response, while HR response is much more variable. This would not incite for the use of HR to guide training intensity in COPD.

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Table 1. Baseline characteristics.

Gender (m/f)	10/1
Age (yrs)	69±6
BMI ($Kg \cdot m^{-2}$)	27±7
FEV_1 (%pred)	42±12
TL_{CO} (%pred)	59±19
6MWT (%pred)	74±18
QF (%pred)	74±11
W_{max} (%pred)	54±17
$V'O_{2max}$ (%pred)	64±33
$V'E_{max}$ (%MVV)	92±26
HR_{max} (%pred)	79±15

Data are presented as mean±SD. m: male; f: female; BMI: body mass index; FEV_1: forced expiratory volume in one second; TL_{CO}: diffusion capacity for carbon monoxide; 6MWT: six minute walking test; QF: quadriceps force; W_{max}: baseline maximal workload; VO_{2max}.: baseline maximum oxygen uptake; V_{Emax}: baseline maximum minute ventilation; HR_{max}: baseline maximum heart rate; MVV: maximal voluntary ventilation.

Table 2. Average time, $V'O_2$, $V'E$ and HR for all exercises from one training session in week 1, 6 and 12.

		Cycling	Leg press	Walking	Arm cranking	Stair climbing
Time (min)	**wk 1**	11±1	2.1±0.7	11±1	2.6±1.0	3.3±1.4
	wk 6	14±0	1.9±0.4	14±1	4.2±0.7	4.3±2.1
	wk 12	14±3	1.8±0.5	12±5	4.5±1.4	4.7±1.8
$V'O_2$ (l/min)	**wk 1**	0.92±0.25	0.62±0.10 †	0.98±0.32	0.71±0.19 †	0.95±0.29
	wk 6	0.97±0.25	0.68±0.11††	1.08±0.35	0.85±0.16 †	0.97±0.29
	wk 12	0.98±0.22	0.76±0.18 †	1.12±0.27	0.90±0.15 †	1.0±0.22
$V'E$ (l/min)	**wk 1**	31±7	22±3 †	32±8	27±7 †	31±8
	wk 6	33±6	25±3 ††	35±8	30±6 *	33±7
	wk 12	33±6	26±5 ††	36±8	31±7 **	36±9
HR (bpm)	**wk 1**	106±15	99±16 ††	109±14	108±15 #	107±15
	wk 6	105±19	99±17††	112±21	113±17 #	109±18
	wk 12	109±21	104±20 °	115±19	117±20 #	113±20

Data are expressed as mean±SD. $V'O_2$: mean oxygen uptake; $V'E$: mean minute ventilation; HR: mean heart rate (for the last three, during the exercise bouts); †$p<0.05$ *versus* cycling, walking and stair climbing; ††$p<0.05$ *versus* cycling, walking, arm cranking and stair climbing; °$p<0.05$ *versus* walking, arm cranking and stair climbing; *$p<0.05$ *versus* walking; **$p<0.05$ *versus* walking and stair climbing; #$p<0.05$ *versus* leg press.

Legends figures

Figure 1: Work rate progression of cycling, leg press resistance training and treadmill walking during the exercise training program. The individual progression of each patient is shown in the figure (dashed lines). The bold dashed lines indicate the progression that was anticipated. W_{max}: baseline maximal work rate; 1RM: baseline one repetition maximum (the maximum load which can be moved only once over the full range of motion without compensatory movements); 6MWT: baseline six minute walking test.

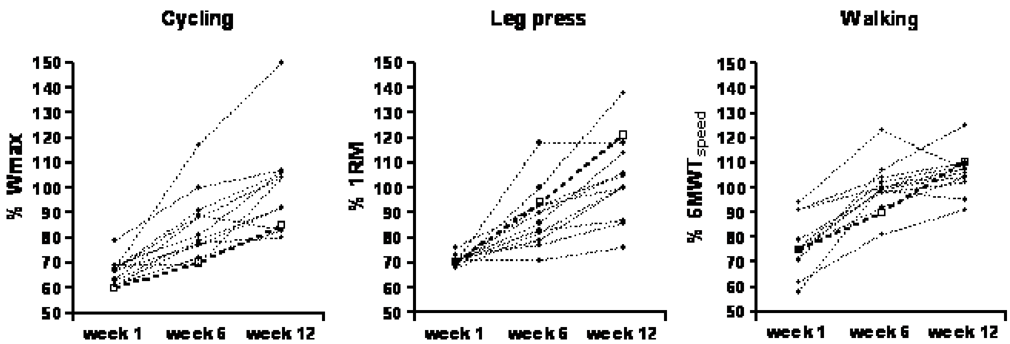


Figure 2: $V'O_2$ (A), $V'E$ (B) and HR (C) in a representative patient during one exercise session in week 1. The straight lines indicate the $V'O_{2max}$ (A), $V'E_{max}$ (B) and HR_{max} (C) achieved during baseline incremental exercise in this patient.

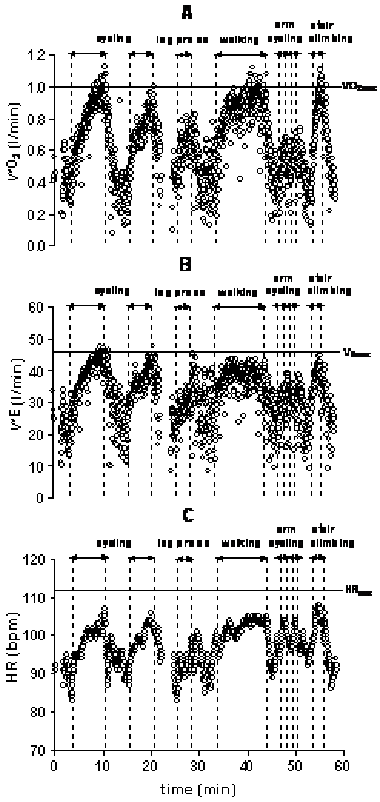


Figure 3: Total exercise time performed in week 1, 6 and 12 (open bars) and time above the thresholds “moderate” (≥40% of *V'*O_2R or HRR) (A) and “hard” (≥60% of *V'*O_2R or HRR (B). Data are expressed as mean ± SD. The increase in exercise time is indicated in the figures (#p<0.05). The dashed lines indicate the average duration of the training sessions (exercise time + resting time). °p=0.12; °°p=0.11; *p=0.059; **p=0.054.

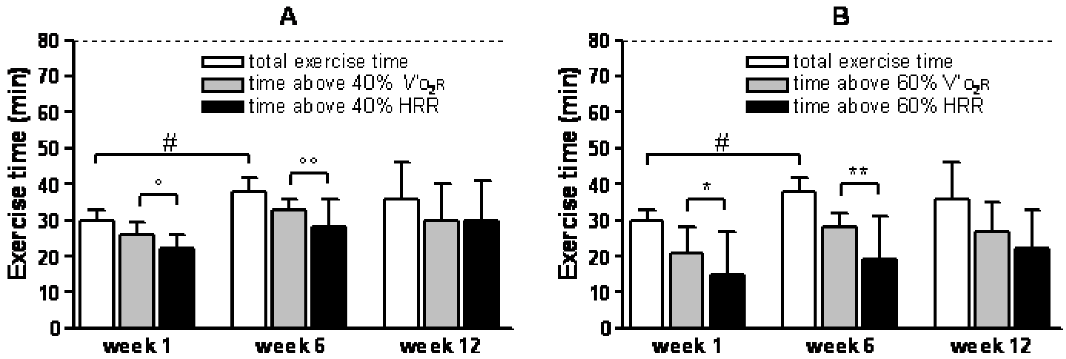
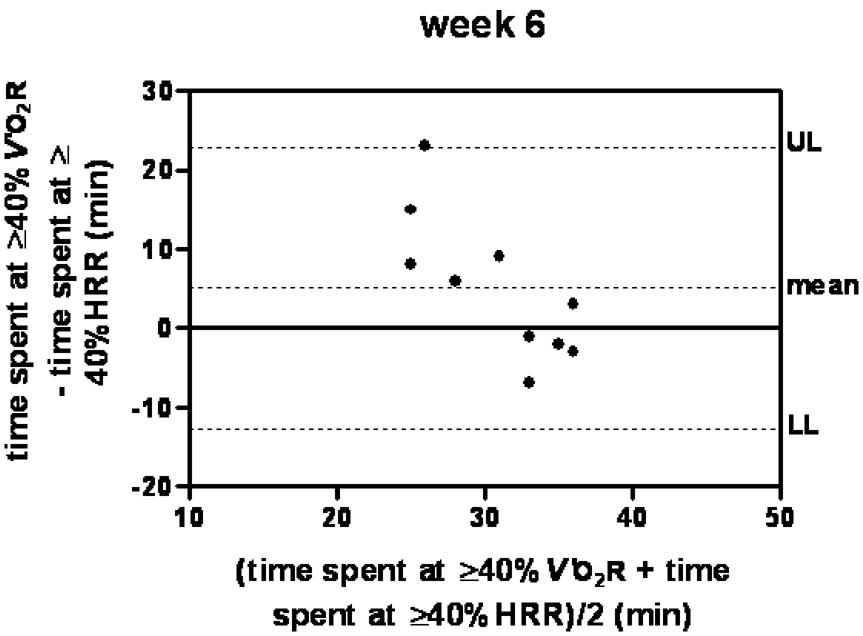


Figure 4: Bland & Altman plot showing the poor agreement between time spent in exercises above 40% of the VO2R and above 40% of the HRR. UL= upper limit (mean + (1.96*standard deviation)); LL= lower limit (mean - (1.96*standard deviation)).


week 6
time spent at ≥40% V̇O₂R - time spent at ≥ 40% HRR (min)
30
20
10
0
-10
-20
10
20
30
40
50
UL
mean
LL
(time spent at ≥40% V̇O₂R + time spent at ≥40% HRR)/2 (min)

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