High-intensity lower limb endurance training in chronic respiratory disease

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Abstract High-intensity endurance training is mainly undertaken during pulmonary rehabilitation for patients with chronic respiratory disease. High-intensity endurance training is recommended in many clinical management guidelines. High-intensity endurance training involves training generally at an intensity of at 60-80% of the patient's peak work capacity or higher. The effects of high-intensity lower limb endurance training have mostly been investigated in chronic obstructive pulmonary disease (COPD) patients. High-intensity endurance training is more effective than low-intensity endurance training in terms of achieving physiologic gains. According to meta-analyses of studies in patients with chronic respiratory disease, this type of training results in improvements in range of exercise measures, health-related quality of life and dyspnea. There is also some evidence to support the benefits of high-intensity endurance training patients suffering from chronic respiratory diseases other than COPD, such as in idiopathic pulmonary fibrosis and pulmonary arterial hypertension patient.

Health Science Research 27 : 1-11, 2015

Key Words : Chronic respiratory disease, Endurance training, High-intensity

Received 31 July 2014

Accepted 10 October 2014

1. Introduction

Recommended guidelines pertaining to pulmonary rehabilitation for patients with respiratory disease have been developed by the American College of Chest Physicians/ American Association of Cardiovascular and Pulmonary Rehabilitation (ACCP/AACVPR) (joint) in 2007, the British Thoracic Society (BTS) in 2013, and, the American Thoracic Society and European Respiratory Society (ATS/ERS) (joint) in 2013, respectively[1-3]. In Japan, a pulmonary rehabilitation manual developed by the four associations (the Japan Society for Respiratory Care and Rehabilitation; the Japanese Respiratory Society; the Japanese Association of Rehabilitation Medicine; and Japanese Physical Therapy Association) was published in 2012.

Endurance training (also referred to as aerobic training) is the cornerstone of pulmonary rehabilitation programs. The BTS 2013 pulmonary rehabilitation guidelines state that high-intensity exercise training improves exercise capacity (evidence level 1++), dyspnea (evidence level 1++), health status (evidence level 1++), psychological functioning (evidence level 1+), and activities of daily living (ADL) (evidence level 1+)[2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published in 2011, includes high level evidence for improved survival following high-intensity endurance training[4]. The effects of endurance training described in many such guidelines are based on studies predominantly in people with Chronic Obstructive Pulmonary Disease (COPD)[1-3].

The effects of endurance training in patients with interstitial lung disease (ILD) in particular idiopathic pulmonary fibrosis (IPF) have also been reported[5-8]. Clinical management guidelines recommend that "the

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majority of patients with IPF should be treated with pulmonary rehabilitation"[9]. The Frequency, Intensity, Time, and Type (FITT Principle) are essential for when prescribing exercise training. In this review, we focus on the intensity component of exercise training in chronic respiratory diseases. However, the limits to exercises in different respiratory diseases may be different in themselves. For example in patients with COPD, exertional dyspnea is one of the main factors limiting. The mechanism for dyspnea in COPD is related to expiratory flow limitation and dynamic hyperinflation. Progressive dyspnea, hypoxaemia, frequently accompanied by a nonproductive cough; is the hallmark symptom and causes exercise limitation in patients with ILD. We focus in particular on the intensity of lower limb endurance training with a particular focus on studies in patients with COPD but also include data derived in patient populations with other chronic respiratory diseases.

2. High-intensity and low-intensity endurance training

The characteristics of high and low-intensity are summarized in Table 1. High-intensity generally refers to exercising at between 60-80% of peak work capacity, or on occasions at intensities in excess of this load. The load prescribed for low-intensity exercise is generally in the range of 40-60% peak work capacity. There are several randomized controlled trials (RCTs) comparing high-intensity training and low-intensity training in patients with chronic respiratory disease.

Casaburi et al. randomized 19 COPD patients to high-intensity or low-intensity training for a period of 8 weeks with training taking place using a cycle ergometer on 5 days each week and examined the physiologic responses. The magnitude of improvement in physiologic responses was significantly greater in those who trained at a high-intensity. For example, minute ventilation ($\dot{V}E$), heart rate (HR), and blood lactate were all reduced by a significantly greater amount at submaximal workload following high intensity compared to low-intensity training[10].

Gimenez et al. randomized 13 COPD patients to high-intensity or moderate-intensity lower limb training daily for a period of 6 weeks[11]. The physiologic measurements (e.g. peak $\dot{V}O_2$ and anaerobic threshold) significantly improved by a greater amount in the high-intensity group. Further, during endurance exercise at a work load of 40 watts, dyspnea scores, blood lactate, $\dot{V}E$, respiratory rate (RR), HR, and O_2 pulse significantly improved in the high-intensity group[11].

Vallet et al. randomized 24 COPD patients to exercise at their HR achieved at the anaerobic or gas exchange threshold (high-intensity) or at a HR equivalent to 50% of maximal cardiac frequency reserve (low-intensity)[12]. In both groups, the program was carried out for 45 minutes, 5 times per week, for 4 weeks using a stationary cycle ergometer. Improved maximum oxygen uptake (peak $\dot{V}O_2$) and O_2 pulse were only observed in the high-intensity group, and $\dot{V}E$ and blood lactate at any given $\dot{V}O_2$ decreased by a greater magnitude in this group more than in the low-intensity group[12]. Although these findings are derived from RCTs they include only a small number of patients, but do provide evidence of physiologic benefits following high-intensity lower limb endurance training. However, although high-intensity training has strong evidence of physiologic benefits, there are no robust data to determine whether high-intensity training has greater benefit on health-related quality of life (QOL), dyspnea and ability to perform ADL, when compared to low or moderate-intensity training.

Table1. High-intensity and low-intensity training

	High intensity	Low intensity
Definition	60 to 80% of peak $\dot{V}O_2$ (peak work rate)	40 to 60% of peak $\dot{V}O_2$ (peak work rate)
Advantages	Large improvements in exercise capacity during same exercise load, maximal physiologic training effects	Easier to continue with this type of training at home exercise Low risk Easier to maintain adherence
Disadvantages	Not all patients can tolerate this training intensity Greater supervision required for risk assessment Poor adherence	Small improvement of exercise capacity Need a long period to appear effect of exercise training
Indication	High motivation No Cor pulmonale, serious arrhythmia, and heart disease. Keep SpO_2 > 90% during exercise training	Severe dyspnea Cor pulmonale Age > 75

$\dot{V}O_2$; oxygen consumption, SpO_2: oxyhemoglobin saturation measured by pulse oximetry

3. High-intensity training in COPD patients

1) Exercise capacity

Various measures of exercise capacity improve following high-intensity training in COPD patients. This is clinically important because exercise capacity (as measured by peak $\dot{V}O_2$ and 6-minute walk distance (6MWD) is a stronger predictor of mortality than pulmonary functions or health-related QOL, and highlights the importance of evaluating exercise capacity in pulmonary rehabilitation programs.

High-intensity training improves peak WR (peak work rate), peak $\dot{V}O_2$, anaerobic threshold, work efficiency, peak V_T (peak tidal volume), peak $\dot{V}_E$ (peak expiratory minute volume), during incremental exercise capacity testing, and also improves the τ of $\dot{V}O_2$ and exercise duration time in constant load exercise testing[2,3,13,14]. Particularly, the reactivity of the effect of the exercise duration time in constant load exercise testing was excellent compared to various other exercise capacity measurements. Improvement of quadriceps force and work efficiency is involved in prolonged exercise duration time due to high-intensity training[14]. The pathophysiologic abnormalities and possible mechanisms for improvement after exercise training of patients suffering from chronic respiratory disease including COPD patients are shown in Table 2[15]. In clinical setting, dyspnea scores are used in order to adjust exercise intensity[16,17]. This is possible because

Table2. Pathophysiologic abnormalities in patients with chronic respiratory disease and possible mechanisms for improvement after exercise training

	Pathophysiologic abnormality	References	Changes with exercise training	References
Body composition	Lower limb muscle cross-sectional area ↓ Fat-free mass ↓ Fat mass ↓ % fat- free mass ↓	54)	Fat-free mass and fat mass with exercise and nutritional supplementation ↑ Fat-free mass and ↑ Fat mass with rehabilitation (resistance + endurance combined enhanced) ↓ Fat-free mass with testosterone and anabolic steroids ↑	55-57)
Lower limb muscle fiber type, size	% Fiber type I and myosin heavy chain (advanced disease) ↓ % Fiber type IIX ↑ Fiber cross-sectional area linked to muscle atrophy ↓	58-64)	Fiber-type proportion = Fiber cross-sectional area ↑	60)
Capillarization	Capillary contacts to fiber cross-sectional area, especially in patients developing fatigue during exercise ↓	60, 65)	Capillary contacts proportional to increase in fiber cross-sectional area ↑	60)
Muscle metabolic capacity	Capacity of oxidative enzymes: citrate synthase, 3-hydroxyacyl-coenzyme A dehydrogenase, succimic acid dehydrogenase, cytochrome c oxidase ↓ Cytochrome c oxidase activity in hypoxemic patients ↑	65-67)	Capacity of oxidative enzymes after endurance training ↑	68)
Metabolism at rest/after exercise	Rest: intracellular pH ↓, Phosphocreatine and adenosine triphosphate ↓, lactate and inosine monophosphate ↑; glycogen stores in hypoxemic patients ↓; glycogen stores related to physical activity level ↓; uncoupling protein-3 content ↓ Exercise: rapid decline in muscle intracellular pH, phosphocreatine/inorganic phosphate even in patients with relatively preserved submaximal oxygen delivery	60, 66, 69-73)	Lactic acidemia at iso work rate Normalization of decline in intracellular pH and phosphocreatine/inorganic phosphate ↓ Faster phosphocreatine -recovery.	10, 70)
Inflammatory state	Inflammatory/apoptotic markers may occur in skeletal muscle in subpopulations of wasted COPD ↑	74, 75)	No effect shown or not studied	
Redox state	Glutathione levels normal to moderately reduced ↑ Oxidative stress in the skeletal muscle of COPD patients after quadriceps exercise	61, 76-78)	Oxidized gluthatione in contrast to observations in healthy subjects ↑ Partially reversed by antioxidant therapy (N-acetyl cysteine)	76)

Source: Reference[15]
pH; potential hydrogen, COPD; chronic obstructive pulmonary disease

of the strong association between dyspnea scores and exercise intensity. Accordingly, dyspnea scores are used to progress intensity throughout a training program[18]. A dyspnea score of 4 to 6 using the Borg then constructed a category ratio 10 scale (the Borg CR10 Scale) or 12 to 14 using a Rating of Perceived Exertion ranging are considered the target for exercise training intensity[17]. Alternatively, HR at the gas exchange threshold or specific training load has also been used[12].

In the 2006 Cochrane review of exercise training in COPD[19], there were 13 trials of pulmonary rehabilitation that included high-intensity training with maximal exercise capacity as the outcome, and a meta-analysis was carried out on 268 patients in the rehabilitation group and 243 patients in the usual care group (non-exercise control group). The common effect (weighted mean difference [WMD]) for the change in maximum workload achieved on a maximal cycle ergometer test (peak WR) following training was 8.43 watts (95% CI: 3.4 to 13.4). Another meta-analysis was carried out on data from 16 trials that used functional exercise capacity (as measured by 6MWD) as the outcome from 346 patients in the rehabilitation group and 323 patients in the usual care group. The common effect WMD for a 6MWD was 48.5m (95%CI: 32 to 65). The minimum important difference (MID) of 6MWD was 54m for the average patient to stop rating themselves as "about the same" and start rating themselves as either "a little bit better" or "a little bit worse" (95% CI: 37 to 71)[20]. The common effect of the Cochrane review does not exceed MID. However, other meta-analysis reports[21] analyzed that 6MWD is 55.7m (95% CI: 27.8 to 92.8) as the effect in the rehabilitation group, which exceeds the MID. 11 trials (413 patients) were included in this analysis. After conversion back to natural units for the 6MWD, a difference in response between the treatment and control groups of 55.7m (95 % CI: 27.8 to 92.8) was found. They estimated the minimal clinically important difference (MCID) of the walk test at about 50m from a study in which COPD patients rated their walking ability by subjective comparisons with one another. The limits of the CI for the pooled estimate of effect size (27.8 to 92.8) were wider than those of the estimate of the MCID of the 6-min walk test (6MWT) (37 to 71).

Griffiths et al reported a study of 200 patients chronic lung disease patients (167 had COPD) were randomly assigned to 6 weeks multidisciplinary rehabilitation program or usual care that did not involve any exercise training[22]. A program involving 30 minutes of walking at an intensity equivalent to 80% of the maximum speed achieved at baseline on the incremental shuttle walk test (ISWT) was undertaken in the exercise training group, and, after 6 weeks, a difference of 75.9m was observed in performance on the ISWT compared to the control group, leading to the conclusion that high-intensity walking training is effective[22]. This improvement exceeds the MID for the ISWT which was reported as 47.5m[23].

2) Health-related quality of life (QOL)

In the 2006 Cochrane review, the effect of high-intensity training was investigated using two health-related QOL measures[19]. There were 11 RCTs that used the Chronic Respiratory Disease Questionnaire (CRQ), with a meta-analysis carried out on data from 326 patients in the rehabilitation group and 292 patients in the usual care group (control). The CRQ comprises the four domains of fatigue, emotional function, mastery, and dyspnea, all of which improved following training. The common effect (WMD) for fatigue was 0.92 (95%CI: 0.71 to 1.13), emotional function was 0.76 (95%CI: 0.52 to 1.00), and for mastery was 0.97 (95%CI: 0.74 to 1.20). For the dyspnea domain, the meta-analysis included data from 323 patients in the rehabilitation group and 287 patients in the usual care group, with the WMD being 1.06 (95%CI: 0.85 to 1.26). All these changes exceeded the MID for CRQ scores is which has been determined as 0.5 points per item[19].

There are 6 RCTs that used the St Georges Respiratory Questionnaire (SGRQ), with meta-analysis carried out using data from 196 patients in the rehabilitation group and 188 patients in the usual care group. SGRQ comprises the domains of, symptoms, impacts, and activity, and provides a total score[19]. The common effect (WMD) for the total score was -6.11 (95%CI: -8.98 to -3.24), symptoms was -4.68 (95%CI: -9.61 to 0.25), impacts was -6.27 (95%CI: -10.08 to -2.47), and activity was -4.78 (95%CI: -7.83 to -1.72) with all these changes exceeding the MID for this scale which is 4 points[24]. The COPD assessment test (CAT) is a health status measure that has recently started to be used to determine responses to pulmonary rehabilitation[25-27].

3) Physical activity

Physical activity is an independent prognostic factor for mortality and hospitalization due to severe exacerbations in COPD patients[28,29]. A recent systematic review and meta-analysis of studies of exercise training was unable to find any published RCTs examining the effect of exercise training compared with usual care[30]. The authors included a total of 7 studies, 2 randomized trials and 5 single-group interventional studies[31,32]. They concluded that current data suggest supervised endurance training may lead to a small but significant effective on physical activity[31].

4. High-intensity training in in respiratory diseases other than COPD

Although there are very clear evidence-based guidelines regarding exercise training for COPD patients, in contrast there are many less reports pertaining to the benefits of exercise training, and in particular recommended training intensity, in patients with other chronic respiratory diseases[33]. In the following sections we have summarized the results of studies of effects of endurance training in patients with other respiratory diseases other than COPD

1) Interstitial lung disease (ILD)

A Cochrane systematic review reported 2 RCTs of effect of exercise training in ILD and interstitial pneumonia (IP)[7]. High-intensity exercise training is used in pulmonary rehabilitation programs for ILD and IPF patients[5,8]. 2 trials provided sufficient data using 6MWD for meta-analysis, with a total of 43 participants in the exercise training group and 42 participants in the control group[7,8]. The common effect (WMD) for change in distance walked was 38.6m in favor of the exercise training group (95% CI: 55.4 to 61.9). The common effect (standardized mean difference) for change in dyspnea was -0.47 in favor of the exercise training group (95% CI: -0.91 to -0.04). There was a common effect indicating an improvement in QOL with exercise training (standardized mean difference 0.58, 95% CI: 0.15 to 1.02).

The magnitude of these benefits was smaller than that generally seen in COPD[7,34]. Kozu et al. reported that PR produced smaller improvements in 6MWD in IPF patients than in COPD patients[34]. They measured exercise capacity by 6MWT for the benefits of high-intensity endurance exercise training. Furthermore Arizono et al. reported that endurance time showed the most striking improvement than peak WR, 6MWD and the incremental shuttle walk distance (ISWD) by evaluating the efficacy of high-intensity endurance exercise training in IPF patients. The effect size of endurance time was as large as 2.96[35]. The improvement in endurance time was significantly correlated with change in the anaerobic threshold and work efficiency.

2) Cystic fibrosis

Exercise training is now an essential component of the management of patients with cystic fibrosis (CF)[36]. A Cochrane systematic review included 28 studies examining the effect of exercise training in patients with CF. Most of the trials that prescribed training in accordance with recommendations from the American College of Sports Medicine, (i.e. exercising for a tolerable time and aiming to progress to at least 20 to 30 minutes exercise at each session, at 55% to 64% maximum HR, on 3 to 5 days a week) demonstrated that training was beneficial[37]. Substantial evidence now confirms that exercise training significantly reduces the rate of decline in lung function in CF patients, at least in part by enhancing mucus clearance[38]. Exercise training has beneficial effects in CF patients with regard to the preservation and improve pulmonary function, exercise capacity, muscle strength and QOL, and reducing morbidity and mortality[39].

3) Non-CF bronchiectasis

Peripheral muscle endurance, exercise capacity, fatigue and health status are adversely affected by in patients with non-CF bronchiectasis[40]. Newell et al. investigated the effects of exercise training in 32 patients with idiopathic bronchiectasis who were randomly allocated to one of three groups (pulmonary rehabilitation plus sham inspiratory muscle training, pulmonary rehabilitation plus 60% inspiratory muscle training of maximum inspiratory pressure and control). The patients underwent 8 weeks training program with exercise performed 3 times each week at an intensity equivalent to 80% of the peak HR. Patients assigned to the exercise training groups demonstrated significant increases in performance on the ISWT equivalent to a change of 96.7m (95% CI: 9.6 to 133.7)[41]. In this study, exercise training resulted in improvements in exercise capacity of a similar in magnitude to that seen in patients with COPD[41]. Furthermore, Lee et al. reported that patients with non-CF bronchiectasis were randomly allocated to 8 weeks of supervised exercise training. Exercise training was included treadmill or land based walking, with the initial intensity set to 75% of the maximal speed achieved on ISWT, stationary cycling prescribed at 60% of maximal WR for cycling. Exercise training group increased the ISWD (mean difference to control 62m, 95% CI: 24 to 101) and 6MWD (mean difference to control 41m, 95% CI: 19 to 63)[42]. However, there are few reports of the exercise training in non-CF bronchiectasis, and more evidence is required[43].

4) **Asthma**

Exercise training as part of pulmonary rehabilitation is provided to patients with asthma as well as those with COPD. Turner et al. investigated the effects of exercise training in 34 patients with asthma were randomly allocated to 6 weeks period of supervised exercise training or a non-exercise control group[44]. Training was performed 3 times each week at an initial intensity equivalent to 80% of the average walking speed achieved on the 6MWT. In this study, 6MWD increased by an average 36 minutes the exercise group[44,45]. There is some evidence to suggest that exercise training may reduce airway inflammation in asthmatics[46]. Furthermore, the pre-exercise use of inhaled bronchodilators and a gradual warm-up are recommended to minimize exercise-induced bronchospasm[3].

5) **Pulmonary arterial hypertension**

A study protocol reported whether outpatient-based, whole body high intensity exercise training is beneficial and safe in individuals with pulmonary arterial hypertension[47]. Intensity for the lower limb endurance exercise was prescribed with the aim of achieving 60-70% HR max (based on age predicted maximum, 220-age), while maintain SpO_2 (oxyhemoglobin saturation measured by pulse oximetry) ≧ 92% and symptom intensity (Borg CR10 scale < 4 and Rating of Perceived Exertion (RPE) < 4). Mereles et al. investigated that the prospective randomized study to evaluate the effects of exercise and respiratory training in patients with severe symptomatic pulmonary arterial hypertension. The exercise training consisted of an interval training using a cycle ergometer with intensity prescribed at a workload equivalent to 60 to 80% of peak HR. The exercise group underwent 15 weeks training program. The mean ± standard deviation improvement in 6MWD in the group who trained was 96 ± 61m[48]. Furthermore there are 2 RCTs that 6MWD was used as outcome in pulmonary hypertension[49,50]. Ley et al. investigated the effects of exercise training in 20 patients were randomly allocated to 3 weeks period of supervised exercise training. Training was performed an initial intensity 60-80% of HR max. In this study, 6MWD increased average 91m in the exercise group[50]. Westein et al. reported that 24 patients with pulmonary hypertension were randomized into 10 weeks program that consisted of patient education only or patient education plus aerobic exercise training. The intensity was 70-80% of HR max. Patients receiving aerobic exercise training plus education resulted in a 53m increase in 6MWT[49]. Exercise training in this patient population seems to be a promising adjunct to medical treatment and may have benefits in terms of survival in patients with chronic thromboembolic pulmonary hypertension[51].

6) **Sequelae of tuberculosis**

The benefit of exercise training in patients of sequelae of tuberculosis appear to be similar to we reported in people with COPD. Ando et al performed a prospective nonrandomized open trial over 9 weeks period[52]. 32 patients with sequelae of tuberculosis and age and forced expiratory volume in one second (FEV_1) matched COPD patients were enrolled in the study. During the high-intensity walking training, each patient was instructed to walk at > 90% of their baseline 6MWT speed. To maintain the selected speed, patients were instructed to cover the prescribed number of rounds of the circuit within a 15 minute period. Following training, 6MWD improved by an average of 40m (sequelae tuberculosis patients 42m, COPD patients 47m). This study showed that the magnitude of improvement in 6MWD following 9 weeks pulmonary rehabilitation program was similar in both patient groups and further, the improvement in 6MWD was maintained for 6 months after the termination of the pulmonary rehabilitation program in both groups[52].

Yoshida et al. investigated the effects of exercise training in 14 patients with stable sequelae of tuberculosis[53] The patients were instructed to perform daily walking training in a hallway within the hospital for 2 weeks. The training commenced at an intensity equivalent to the patients' maximum walking speeds achieved during a baseline treadmill test. The training was started their maximum walking speed during the treadmill test. Exercise tolerance improved following training as demonstrated by a significant increase in peak oxygen uptake (1.2ml/kg/min) and 6MWD (68m) [53].

5. Conclusion

High-intensity lower limb endurance training in patients with chronic respiratory disease including COPD significantly improves exercise capacity, dyspnea, and health-related QOL. High-intensity training is associated with a greater magnitude of physiologic response than low -intensity training; however, there is less evidence to support greater benefits in symptoms and health-related QOL with high versus low-intensity training. Evidence demonstrating the efficacy of high-intensity endurance training in patient populations other than COPD, for example ILD, cystic fibrosis, asthma and pulmonary arterial hypertension is being accumulated.

6. Acknowledgments

We thank to Sue Jenkins, PhD, Associate Professor at the School of Physiotherapy and Exercise Science, Curtin University (Perth, Western Australia) for help in reviewing this manuscript.

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