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J Appl Physiol 107:971-976, 2009. First published 2 April 2009;
doi: 10.1152/japplphysiol.91459.2008

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J Appl Physiol 107: 971–976, 2009.
First published April 2, 2009; doi:10.1152/japplphysiol.91459.2008.

HIGHLIGHTED TOPIC | *The Respiratory Muscles in Chronic Obstructive Pulmonary Disease*

Response of the respiratory muscles to rehabilitation in COPD

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Submitted 7 November 2008; accepted in final form 26 March 2009

Decramer M. Response of the respiratory muscles to rehabilitation in COPD. *J Appl Physiol* 107: 971–976, 2009. First published April 2, 2009; doi:10.1152/japplphysiol.91459.2008.—Respiratory rehabilitation is known to improve outcomes in patients with chronic obstructive pulmonary disease (COPD). The question addressed in the present review is whether these beneficial effects are related to improvements in inspiratory muscle function. Respiratory muscle fatigue often did not occur during exercise in patients with COPD, since exercise limitation usually occurred when significant force reserve in the inspiratory muscles was still present. Notwithstanding, a number of observations may provide indirect evidence that respiratory muscle fatigue may occur during exercise. Some evidence is present that, in normal humans, whole body exercise training improved inspiratory muscle endurance, but no studies are available in patients with COPD. Animal studies invariably demonstrated that exercise training increased the number of oxidative fibers and oxidative enzyme activity in inspiratory muscles. These effects, however, were considerably smaller than the effects found on peripheral muscles with similar fiber composition. Clear evidence indicated that inspiratory muscle training (IMT) improved inspiratory muscle function. Two large meta-analyses indicated that, if the training load was properly controlled, IMT alone or combined with general exercise reconditioning improved inspiratory muscle strength and endurance and dyspnea. The combination did not result in greater improvements in functional exercise capacity. Animal studies and one patient study confirmed the occurrence of structural remodeling of the inspiratory muscles in response to IMT. The final question is whether improvements in inspiratory muscle function produced by IMT lead to improved outcomes in COPD. In all five studies in which training load was adequately controlled, a significant reduction of dyspnea during activities of daily living was found. Eight randomized studies examined the effects of the combination. Greater improvements in exercise capacity were only found in three studies, and none showed a greater reduction in dyspnea.

chronic obstructive pulmonary disease; respiratory rehabilitation; respiratory muscles; exercise capacity

THE BENEFITS OF RESPIRATORY rehabilitation programs in patients with chronic obstructive pulmonary disease (COPD) are well established now. A recent meta-analysis of 31 trials performed in this field corroborated that pulmonary rehabilitation programs improved exercise tolerance and health-related quality of life (33). The effects on health-related quality of life were large, exceeding the clinically important difference of 0.5 units in all domains, whereas the effects on functional exercise capacity were smaller and at or slightly below the clinically important difference [48 m (34, 69)]. In addition, a reduction in the use of medical resources was noted in several trials (22, 75). At present, an effect on mortality has not been convincingly demonstrated (68). Respiratory rehabilitation programs usually consist of a multidisciplinary intervention composed of exercise training, psychosocial support, nutritional intervention, education, and vocational therapy. It is generally accepted that the most effective components of these programs are exercise reconditioning and psychosocial support (34).

Since in 1976 Leith and Bradley demonstrated in normal subjects that both strength and endurance training of the respiratory muscles were practically possible in normal humans (39), respiratory muscle training received considerable attention in patients with COPD as well. The purpose of the present mini-review is to review the role of the respiratory muscles in respiratory rehabilitation, which remains controversial after more than 40 years of research. We will limit this review to inspiratory muscles and inspiratory muscle training (IMT), although scant studies were performed on the expiratory muscles as well (48, 79, 80). This will be done by means of four key questions. Does respiratory muscle fatigue contrib-

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ute to exercise limitation in COPD? Do the respiratory muscles respond to exercise training? Do the respiratory muscles respond to specific respiratory muscle training? What is the relationship between respiratory muscles and outcomes in patients with COPD?

DOES RESPIRATORY MUSCLE FATIGUE CONTRIBUTE TO EXERCISE LIMITATION IN COPD?

Exercise limitation in COPD patients has been intensely studied in the last decades. It is still the subject of a lively debate. In patients with advanced COPD, exertional symptoms limit exercise capacity before physiological maxima are reached. Dyspnea is usually the main limiting symptom. The development of dyspnea is related to dynamic hyperinflation and mechanical restriction, such as expanding tidal volume and obtention of minimal inspiratory reserve volume. Accordingly, patients stop exercising predominantly because of dyspnea. This is confirmed by the study of Laveneziana et al., who studied 403 COPD patients recently enrolled in multinational clinical trials (37). Sixty-three percent of these patients stopped exercising because of dyspnea. One of the important concepts that emerged from recent research is that of dynamic hyperinflation, whereby progressive increases in end-expiratory lung volume occur, which limit the capacity to further expand tidal volume during exercise and, hence, lead to failure of the ventilatory system (4, 52, 53).

This hyperinflation causes shortening of the diaphragm, so that the muscle develops lower force and generates smaller pressure during contraction (12). Acute hyperinflation also reduces the pressure-generating capacity of the inspiratory intercostal muscles. In chronic hyperinflation, however, the inspiratory muscles may adapt by drop-out of sarcomers, such that, at a given lung volume pressure, generation is well preserved or even increased (10, 72). This is not the case in acute hyperinflation. Chronic loading of the diaphragm, as in COPD patients, also produces adaptations in the muscle. Indeed, Levine et al. demonstrated increases in slow myosin heavy chains I, and decreases in fast myosin heavy chains IIa and IIb in these patients (40). These are generally believed to be adaptations to chronic overload. In the present context, we will focus on respiratory muscle fatigue as a potential cause of exercise limitation. We acknowledge, however, that, in COPD patients, other factors besides dyspnea, mechanical constraint, and ventilatory limitation (see above) may contribute to exercise limitation. These factors include peripheral muscle dysfunction (13) and inappropriate increase in energy demands due to recruitment of abdominal muscles (1).

Critical studies using phrenic nerve twitches were not able to demonstrate signs of diaphragmatic fatigue during exhaustive exercise in patients with COPD (45, 55). A number of recent indirect observations, however, would indirectly suggest that the limits of the respiratory muscle force-generating capacity may be reached at end exercise in COPD patients. First, Kyroussis et al. (32) observed rib cage predominance in the breathing pattern of COPD patients walking to exhaustion, and, concomitantly, they observed slowing of the maximal relaxation rate of esophageal sniff pressure (31). As the same authors did not observe changes in twitch diaphragmatic pressure under these conditions, these observations may signal the occurrence of inspiratory accessory muscle fatigue, although no direct demonstration of such fatigue was made. Along these lines, the same group also demonstrated attenuation of the slowing of maximal relaxation rate of sniff esophageal pressure with pressure support ventilation (56).

Second, Harms et al. demonstrated in healthy trained cyclists that unloading the respiratory muscles by proportional assist ventilation (PAV) increased leg blood flow and exercise performance (23, 24). In other words, at maximal exercise, respiratory muscle blood flow would become exceedingly high and would compete with leg blood flow. Accordingly, another study by the same group showed that PAV prevented the exercise-induced diaphragm fatigue demonstrated by phrenic nerve stimulation in normal subjects (2). It is unclear whether these observations made in healthy subjects are applicable to patients with COPD.

Finally, several studies recently demonstrated improvements in exercise dyspnea (46), walking distance, and exercise endurance time in COPD patients with a variety of techniques of ventilatory support, whether it be pressure support ventilation (30), noninvasive nasal ventilation (76), or PAV (7, 16). All of the above observations may be interpreted as evidence of inspiratory muscle fatigue during exercise in patients with COPD potentially limiting exercise capacity. They may, however, also be interpreted in other ways as relieving dyspnea as the prime factor causing exercise limitation (see above).

DO THE RESPIRATORY MUSCLES RESPOND TO EXERCISE TRAINING?

Since exercise increases ventilation by more than 12-fold (18), it is expected that exercise training would constitute a training load to the respiratory muscles. Hence, training-induced improvements in performance would be expected. In general, such adaptations have been found in the guinea pig and rat diaphragm. Indeed, Faulkner and colleagues demonstrated that running resulted in a 13–20% increase in the number of highly oxidative fibers in the costal diaphragm of guinea pigs (17, 42). Moore and Gollnick (47) and Ianuzzo et al. (29) confirmed these findings and found that running increased Krebs cycle enzyme activity in the rat costal diaphragm by 30%. This was later confirmed by Powers and colleagues (38, 59–64), who demonstrated that endurance and high-intensity interval training both increased citrate synthase activity in the costal diaphragm in rats. Since generation of ATP via oxidative phosphorylation results in formation of free radicals and hyperperoxides, training is also expected to increase the levels of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase. Increases in the levels of the two former enzymes, but not in the latter, were found in the costal diaphragm (59). In this context, a well-known observation is that the increases in oxidative enzymes with training in the diaphragm (20–30%) are considerably smaller than those observed in locomotor muscles with a similar fiber composition, such as the plantaris (40–80%) (58). This would suggest that exercise training places a smaller metabolic demand on the diaphragm than on the locomotor muscles. In addition, the increases in oxidative capacity in the diaphragm appear to be unrelated to exercise workload, in contrast to those of locomotor muscles. This is likely to be related to the fact that the diaphragm reaches a plateau in motor unit recruitment early in exercise, and that any further increase

in ventilation at higher workloads is due to recruitment of additional ventilatory muscles (73). On the basis of this observation, and if similar concepts were to apply in patients with COPD, a greater effect of exercise training on the peripheral muscles would be expected. Conversely, IMT might be useful in combination with exercise training to further improve the endurance capacity of the diaphragm (see below).

In contrast to the multitude of studies in rodents, only scant studies have addressed this question in humans (11, 54, 69). These studies suggest that whole body exercise training in normal subjects resulted in improved respiratory muscle function. In two studies, it was shown to improve ventilatory muscle endurance as evidenced by elevated, sustained ventilation (54, 69). In the third study, a decrease in maximal inspiratory pressure (PI_{max}) after maximal exercise was present in untrained subjects, but not in highly trained cross-country skiers (11). No studies, however, are present in COPD patients.

DO THE RESPIRATORY MUSCLES RESPOND TO SPECIFIC RESPIRATORY MUSCLE TRAINING?

Several methods for specific respiratory muscle training have been used. These included methods that predominantly increase muscle strength, such as targeted resistive breathing (5, 25) and threshold loading (36, 50), as well as methods that predominantly increase muscle endurance, such as isocapnic hyperpnea (3, 41, 71). We will not discuss the methodology used in detail in the present review. In terms of the demonstrated functional responses to IMT, two meta-analyses are of paramount importance.

The first by Smith et al. included 17 randomized trials out of 73 articles retrieved (74). Study quality was assessed, and descriptive information regarding study populations, interventions, and outcome measurements were extracted. Across all included studies, effect sizes were as follows: PI_{max} 0.12, $P = 0.38$; inspiratory muscle endurance 0.21, $P = 0.14$; exercise capacity −0.01, $P = 0.43$; functional exercise capacity 0.20, $P = 0.15$; and functional status 0.06, $P = 0.72$. This analysis, however, took all studies into account, regardless of whether or not training load was controlled during inspiratory resistive loading. Secondary analysis suggested that, if this was done, inspiratory muscle strength and endurance might be more consistently improved.

The second study by Lötters et al. more carefully included patients in whom training load was adequate during training, restricting intake to 15 studies employing loads of at least 30% of PI_{max} (44). On the basis of a methodological framework, a critical review was performed, and summary effect sizes were calculated by applying both fixed and random effect models. This approach more clearly demonstrated effects of IMT. Indeed, both IMT alone and IMT combined with general exercise reconditioning significantly increased inspiratory muscle strength and endurance. Dyspnea was reduced both at rest and during exercise. A trend for an improved functional exercise capacity was present with IMT, combined with general exercise reconditioning, but it did not reach statistical significance. Training effects did not correlate with patient characteristics, such as degree of severity of COPD or hyperinflation.

A word of caution is required in relation to the interpretation of the two meta-analyses. Statistically significant heterogeneity was present in the first meta-analysis, particularly in exercise capacity and functional status. In addition, meta-analyses are associated with a number of methodological problems, including differences in populations, study design, duration of trials, collection of data, drop out, etc. A large prospective randomized study would be far better to judge on the usefulness of IMT. Such a study needs to be done in the future.

However, subgroup analysis in IMT with exercise training demonstrated that patients with inspiratory muscle weakness improved significantly more than patients without (44). This observation may be of more general interest. Indeed, so far, studies have included all COPD patients, instead of directing them toward COPD patients whose outcomes are more likely related to inspiratory muscle function. Some phenotypes defined by stage of COPD, presence of inspiratory muscle weakness, degree of hyperinflation, severity of dyspnea, level of exercise intolerance, and reduced health status may be important determinants of the response to IMT. In addition, in the published studies, a disconnect is observed between the positive effects on dyspnea and the absence of an effect on exercise tolerance. This is surprising, as dyspnea is one of the most important factors limiting exercise tolerance (see above). This discrepancy requires further investigation in the future. In any event, an effect of IMT on dyspnea is expected on the basis of the pathophysiological observations made by Redline et al. (66). Indeed, they demonstrated in normal subjects that the sensation of respiratory force was tightly related to the fraction of PI_{max} used in breathing maneuvers. Hence, increasing PI_{max} is expected to reduce the sensation of respiratory force. Whether the same concepts apply to patients with COPD is not clear at present.

Two additional lines of evidence would support the beneficial effect on inspiratory muscle function with properly controlled IMT. First, Bisschop et al. (8) and Gayan-Ramirez et al. (19) demonstrated in an elegantly designed animal model in rats that intermittent resistive loading resulted in type II fiber hypertrophy in the diaphragm. Second, Ramirez-Sarmiento et al. (65) obtained the same result in the external intercostal muscles in COPD patients following 5 wk of resistive loading. These studies demonstrated that structural remodeling of the inspiratory muscles occurred with IMT.

The general conclusion appears to be that, if properly applied, IMT improves inspiratory muscle function, particularly

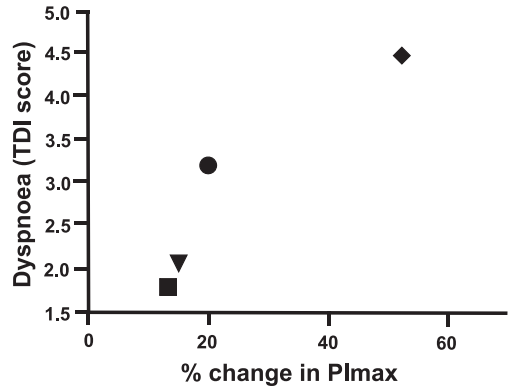

Fig. 1. Relationship between improvement in dyspnea and percent change in maximum inspiratory pressure (PI_{max}) in four studies using transitional dyspnea index (TDI) as an outcome measurement (61–64).

in those patients with weak inspiratory muscles. Whether this improvement in function is simply better performance in a test (57) or leads to improvements in outcome variables in patients with COPD is discussed below.

WHAT IS THE RELATIONSHIP BETWEEN RESPIRATORY MUSCLE FUNCTION AND OUTCOMES IN PATIENTS WITH COPD?

Although improvements of inspiratory muscle function with IMT appear to be likely, the more important question for the clinical applicability of this treatment modality is how improvements in inspiratory muscle function relate to outcomes in patients with COPD. Besides lung function, several other outcomes, including patient-reported outcomes, are now commonly studied in COPD studies. They include the following: dyspnea at rest and during exercise using Borg score, baseline dyspnea index (BDI)/transitional dyspnea index (TDI), or medical research council scale, quality of life measured with the chronic respiratory diseases questionnaire (CRQ) or St. Georges' respiratory questionnaire, maximal exercise capacity, functional exercise capacity, endurance of a submaximal workload, etc. Does IMT improve some of these outcomes considered to be clinically relevant?

Several studies have addressed this question. In general, the interpretation of these studies is hampered by small sample size (ranging from 7 to 39) (20), lack of control, lack of adequate sham intervention, relatively small effect size, lack of intention to treat analysis, lack of double-blinding, migration bias, and lack of balance of the groups at baseline. A large well-designed study could still be very useful in this area. The results of the studies on health status have been somewhat variable, but a recent meta-analysis on the effects of IMT concluded that the effects on health-related quality of life were not conclusive (20). Also, very few and only small studies are available on potential effects on maximal work rate and functional exercise capacity.

Not surprisingly, the effect on the sensation of dyspnea has been studied most. To date, only seven randomized, controlled trials performed in isolation have examined the effects on CRQ, BDI/TDI, or Borg scores. Of these, only five utilized appropriate training loads (15, 43, 70, 71). They also all reported significant reductions in dyspnea during activities of daily living. In the four studies using TDI, there appeared to be an association between the improvement in inspiratory muscle strength and the reduction in dyspnea ($r = 0.94$, $P = 0.06$) (27). It should be noted that this relationship is based on a very small number of data points and is not really statistically significant. This relationship is shown in Fig. 1. Accordingly, a recent study by Hill et al. (28) using an 8-wk program of interval-based, high-intensity IMT, which produced a 29% increase in $P_{I_{max}}$, showed a significant reduction in the dyspnea dimension of the CRQ. Also, a small increase (+27 m) in 6-min walking distance was observed, while no changes in exercise capacity were present.

As whole body exercise programs are now widely used in COPD, the more important question, in fact, may be, does IMT add to the effects of exercise training? Eight randomized studies have been conducted on this topic (6, 9, 14, 21, 35, 77, 78, 81) [reviewed by Hill and Eastwood (26)]. Seven of these eight studies reported significant additional improvements in inspiratory muscle function (9, 14, 21, 35, 77, 78, 81). Three reported greater improvements in exercise capacity in the combined group (14, 77, 78). The effects were relatively small in perspective of the clinical important difference. This difference was not retrieved in the recent meta-analysis of Lötters et al. (44). Dyspnea during exercise and/or activities of daily living was only studied in three of those studies (6, 35, 77). In none of those studies did the effect of the combined treatment surpass the effect of whole body exercise training alone. A recent review of meta-analyses adds to the study of this question (51). Results showed significant improvements in $P_{I_{max}}$ (one meta-analysis) and maximum exercise tidal volume in the IMT plus exercise group (four meta-analyses). No meta-analysis updates were present for dyspnea (51). As a whole, the effects of combining IMT to whole body exercise thus seem to be limited. In this perspective, the place of IMT in pulmonary rehabilitation programs is still open to question. This is why in recent guidelines the place of IMT in pulmonary rehabilitation could not clearly be defined (49), although, in other recent guidelines, IMT was recommended in selected patients with decreased inspiratory muscle strength and breathlessness, despite optimal medical therapy (67).

SUMMARY

The role of IMT in respiratory rehabilitation remains controversial. This is particularly due to the absence of clear data on the effects of IMT on outcomes in patients with COPD, such as exercise capacity, functional exercise capacity, and dyspnea during activities of daily living. Large, randomized studies properly designed methodologically are unfortunately not available. It would be particularly important to demonstrate that the addition of IMT to general exercise training would result in greater benefits than exercise training alone. This has not been done convincingly thus far. Future studies would also need to be directed toward patients who are more likely to benefit from IMT, such as patients with low inspiratory muscle force.

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