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PRO AND CON EDITORIALS

The case for inspiratory muscle training in COPD

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I speak not to disprove what Brutus spoke,
But here I am to speak what I do know.
William Shakespeare. *Julius Caesar*.
Act 3, Scene 2, line 100–101.

Pulmonary rehabilitation is a cornerstone for the management of chronic obstructive pulmonary disease (COPD), since treatments other than smoking cessation and long-term oxygen therapy are merely symptomatic [1]. The current recommendations in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines are that all stages of the disease may benefit from such programmes [1]. The most effective component of these programmes is peripheral (preferably lower limbs) muscle exercise training, whereas the role of inspiratory muscle training (IMT) of patients with stable COPD remains controversial [2–5].

The American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation suggested that ''although the data are inconclusive, IMT could be considered as adjunctive therapy in pulmonary rehabilitation, primarily in patients with suspected or proven respiratory muscle weakness'' [4]. The Joint American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation evidence-based clinical practice guidelines panel [5], (including some of the most respected contributors to the previous statement [4]) recommended that ''IMT be considered in selected patients with COPD who have decreased inspiratory muscle strength and breathlessness despite receiving optimal medical therapy.'' That panel suggested that a large-scale, multicentre randomised controlled trial (RCT) should be performed with appropriate statistical power to more completely examine the role of IMT in treating patients with COPD, concluding that ''the scientific evidence does not support the routine use of IMT as an essential component of pulmonary rehabilitation'' (grade of recommendation 1B) [5]. However, why should ''inconclusive data'' [4] or ''grade of recommendation 1B'' [5] be considered synonymous with ''ineffective'', or prevent a treatment modality in the individual patient [6]? Clinical practice should be based on the best scientific evidence, which does not always correspond to the still discussed evidence based medicine (EBM), involving the use of guidelines and meta-analyses as a basis for clinical approach [7, 8]. In other words, does our medical practice have to be limited to EBM? For example, certainly all readers of this journal use long-term bronchodilators (alone and/or in combination) in the standard comprehensive treatment of stable COPD patients, an approach suggested by all guidelines [1]. Are we sure that IMT is less justified than such pharmacological therapy in these patients? In the following paragraphs we will briefly parallel pathophysiological bases, physiological effects and clinical results of these two therapeutic tools for patients with stable COPD, trying to answer some key questions [3].

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PATHOPHYSIOLOGICAL BASIS

Question

Does airway obstruction or inspiratory muscle weakness contribute to exercise limitation in COPD?

Answer

1) There is evidence that in COPD patients airway obstruction related static hyperinflation leads to further increases in operational lung volumes (dynamic hyperinflation), resulting in exertional dyspnoea [9]. Therefore, there is a pathophysiological basis for the use of drugs reducing airway obstruction (bronchodilators).

2) Peripheral muscle weakness is observed in stable COPD patients of different GOLD stages [10]. This is the pathophysiological basis justifying the recognised effective limb muscle exercise training [4, 5]. Similarly inspiratory muscle weakness is observed in COPD patients, whereas evidence for chronic inspiratory muscle fatigue is weaker [3, 11]. Due to hyperinflation, the shortened diaphragm develops lower force (smaller pressure) during contraction, contributing to dyspnoea and reduced exercise tolerance [12]. It has been recently suggested that during intense exercise in COPD, reduction of respiratory (intercostals) muscle perfusion, but preservation of limb (quadriceps) muscle blood flow, along with attainment of a plateau in cardiac output, may represent the inability of the circulatory system to satisfy the energy demands of both locomotor and respiratory muscles [13]. In contrast, studies in these patients have shown diaphragmatic adaptations to greater oxidative capacity and resistance to fatigue [14]. Therefore, there is a pathophysiological basis for the use of a tool improving inspiratory muscle function.

PHYSIOLOGICAL EFFECTS

Question

Does airway obstruction improve with bronchodilators? Do the inspiratory muscles respond to specific training?

Answer

1) COPD is defined as ''a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible…'' [1]. This means that by definition the specific physiological result of a drug (bronchodilation) is not fully effective in stable COPD. Nevertheless, clinical studies indicate the usefulness of long-term bronchodilators (and these drugs are actually used) in stable COPD [1, 15].

2) Principles of both strength and endurance muscle training, including specificity and intensity, apply also to inspiratory muscles [16]. ''Specificity'' means that the produced training effect is related to the training stimulus, *i.e.* strength training (high intensity and low number of repetitions) will mostly improve strength, while endurance training (low intensity and high number of contractions) will improve endurance. Indeed, in the current issue of the *European Respiratory Journal*, GOSSELINK *et al.* [17] present a meta-analysis of 32 RCTs in these patients, which shows that IMT improves inspiratory muscle strength and endurance. There are also data on mechanisms underlying these effects. IMT enhances pulmonary oxygen uptake kinetics and high intensity exercise tolerance in humans, indicating that the enhanced exercise tolerance following IMT might be related, at least in part, to improved oxygen dynamics [18], thus potentially providing an answer for the suggested inability of the circulatory system to satisfy the energy demands of respiratory muscles [13]. Furthermore, the efficacy of IMT in inducing rib cage muscle remodelling is addressed unequivocally in the landmark study by RAMIREZ-SARMIENTO *et al.* [19] who observed structural adaptations in external intercostal muscles following IMT in patients with COPD. Therefore IMT has specific physiological effects.

CLINICAL RESULTS

Question

Many trials measure the impact of an intervention on surrogate outcomes, such as maximal inspiratory pressure (MIP) by IMT or forced expiratory volume in 1 s (FEV_1) by bronchodilators, but patients and clinicians are far more interested in clinical outcomes including mortality and health-related quality of life (HRQoL) [20]. What is the relationship between bronchodilators or IMT and outcomes in patients with COPD?

Answer

1) Long-term bronchodilators are routinely used, with a wide literature regarding their clinical effects on many outcome measures [1, 21, 22], despite the definition of ''airflow limitation that is not fully reversible.'' [1] and the fact that a patient's FEV_1 response to short-term bronchodilator does not predict long-term response to bronchodilator therapy, and may vary from day to day [23].

2) The meta-analysis [17] was performed also in studies with comparison of IMT with a sham control intervention as requested by [5] and revealed all statistically significant improvements in functional exercise capacity, dyspnoea and HRQoL. Inspiratory muscle endurance training was shown to be less effective than inspiratory muscle strength training. The conclusion was that in patients with inspiratory muscle weakness, the addition of IMT to a general exercise training programme improved MIP and tended to improve exercise performance [17], confirming a previous meta-analysis [24]. Data on mortality are inconclusive both for IMT and bronchodilators [21, 22]. Although the schedule and the maintenance strategy of this modality should be further evaluated, there are conditions like surgery in which ''early pre- and post-operative rehabilitation should be recommended, since it may produce functional benefits in resectable lung cancer patients'' [25]. Such conditions would probably benefit from a short-term perioperative programme of IMT [26]. Therefore, there is evidence for the effect of IMT, at least in selected COPD patients, which is unavailable for many commonly used therapeutic tools, such as many of the drug and ventilatory strategies used in COPD [1, 27].

In conclusion, there is physiological evidence that inspiratory muscle weakness is a clinical feature of COPD (some COPD phenotypes?) patients, with weaker evidence of inspiratory muscle fatigue during exercise in patients with COPD potentially limiting exercise capacity. There are physiological laboratory studies indicating that, if properly applied, IMT improves inspiratory muscle function, particularly in those patients with weak inspiratory muscles. RCTs and meta-analyses indicate that IMT may be an effective treatment modality in COPD patients to improve respiratory muscle strength and endurance, resulting in reduction of dyspnoea and improvement in functional exercise capacity and HRQoL, especially when considering IMT in addition to general exercise training.

Following the previous issues, we can conclude that, at least in selected patients with stable COPD, the evidence of effectiveness of IMT, a low cost modality of pulmonary rehabilitation with no known side-effects, is not lower and potential adverse side-effects are not higher than for long-term bronchodilators, a well recognised long-term therapy in this condition. Clinicians should offer the best care for their patients by recognising the need for evidence, appropriately interpreting the quality of evidence, and taking into consideration patients' values and preferences in the decision-making process [7, 8], without excluding any potentially useful tool.

STATEMENT OF INTEREST

A statement of interest for N. Ambrosino can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES

1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (updated 2009). Bethesda, National Heart, Lung and Blood Institute, 2009. www.goldcopd.com Date last accessed: 2010. Date last updated: 2009.
2 Ambrosino N, Casaburi R, Ford G, *et al.* Developing concepts in the pulmonary rehabilitation of COPD. *Respir Med* 2008; 102: Suppl. 1, S17–S26.
3 Decramer M. Response of the respiratory muscles to rehabilitation in COPD. *J Appl Physiol* 2009; 107: 971–976.
4 Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.

5 Ries AL, Bauldoff GS, Carlin BW, *et al.* Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest* 2007; 131: 4–42.
6 Rossi A. Noninvasive ventilation has not been shown to be ineffective in stable COPD. *Am J Respir Crit Care Med* 2000; 161: 688–691.
7 Karanicolas PJ, Kunz R, Guyatt GH. Point: evidence-based medicine has a sound scientific base. *Chest* 2008; 133: 1067–1071.
8 Tobin MJ. Counterpoint: evidence-based medicine lacks a sound scientific base. *Chest* 2008; 133: 1071–1074.
9 Macklem PT. Therapeutic implications of the pathophysiology of COPD. *Eur Respir J* 2010; 35: 676–680.
10 Seymour JM, Spruit MA, Hopkinson NS, *et al.* The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J* 2010; 36: 81–88.
11 Polkey MI, Kyroussis D, Hamnegard CH, *et al.* Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 154: 1310–1317.
12 De Troyer A, Wilson TA. Effect of acute inflation on the mechanics of the inspiratory muscles. *J Appl Physiol* 2009; 107: 315–323.
13 Vogiatzis I, Athanasopoulos D, Habazettl H, *et al.* Intercostal muscle blood flow limitation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2010; 182: 1105–1113.
14 Levine S, Nguyen T, Kaiser LR, *et al.* Human diaphragm remodeling associated with chronic obstructive pulmonary disease: clinical implications. *Am J Respir Crit Care Med* 2003; 168: 706–713.
15 Celli BR, Thomas NE, Anderson JA, *et al.* Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease. Results from the TORCH study. *Am J Respir Crit Care Med* 2008; 178: 332–338.
16 Leith DE, Bradley M. Ventilatory muscle strength and endurance training. *J Appl Physiol* 1976; 41: 508–516.
17 Gosselink R, De Vos J, van den Heuvel SP, *et al.* Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J* 2011; 37: 416–425.
18 Bailey SJ, Romer LM, Kelly J, *et al.* Inspiratory muscle training enhances pulmonary O_2 uptake kinetics and high-intensity exercise tolerance in humans. *J Appl Physiol* 2010; 109: 457–468.
19 Ramirez-Sarmiento A, Orozco-Levi M, Guell R, *et al.* Inspiratory muscle training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 1491–1497.
20 Cazzola M, MacNee W, Martinez FJ, *et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416–469.
21 Celli B, Decramer M, Kesten S, *et al.* UPLIFT study investigators. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 180: 948–955.
22 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
23 Hanania NA, Ambrosino N, Calverley P, *et al.* Treatments for COPD. *Respir Med* 2005; 99: Suppl. 2, S28–S40.
24 Geddes EL, O'Brien K, Reid WD, *et al.* Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respir Med* 2008; 102: 1715–1729.
25 Brunelli A, Charloux A, Bolliger CT, *et al.* ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 2009; 34: 17–41.
26 Ambrosino N, Gabbrielli L. Physiotherapy in the perioperative period. *Best Pract Res Clin Anaesthesiol* 2010; 24: 283–289.
27 Kolodziej MA, Jensen L, Rowe B, *et al.* Systematic review of noninvasive positive pressure ventilation in severe stable COPD. *Eur Respir J* 2007; 30: 293–306.