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Lung Hyperinflation in Chronic Obstructive Pulmonary Disease: Clinical and Therapeutic Relevance

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ABSTRACT

Patients with chronic obstructive pulmonary disease (COPD) develop lung hyperinflation due to limited expiratory flow, loss of elastic recoil of the lungs or the combination of both, a circumstance that can become intensified during exercise. The increased operating lung volumes, both at rest and during exercise, overload the inspiratory muscles and limit the capacity for lung expansion, resulting in a neuro-mechanical uncoupling that generates or intensifies dyspnoea and limits exercise tolerance. In addition, lung hyperinflation can contribute to cardiovascular dysfunction during exercise and be a risk factor for the development of lung cancer. Bronchodilators are effective for reducing lung hyperinflation, both in static and dynamic situations, and other therapeutic alternatives are also available. In short, lung hyperinflation is a treatable trait of COPD with an important clinical and prognostic impact that requires specific attention. **(BRN Rev. 2019;6(1):67-86)**

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent disorder characterised by several degrees of inflammation and damage to the large and small peripheral airways, alveoli and adjacent capillary networks[1,2]. This results in expiratory flow limitation (EFL), which is conventionally assessed by spirometry to identify airflow limitation[3]. However, the characteristic changes in COPD can generate other functional alterations, including lung hyperinflation (LH). The increased lung distensibility caused by the lower elastic recoil due to lung parenchyma damage, EFL or the combination of both determines an abnormal increase in gas in the lungs and airways at the end of tidal expiration. This circumstance can be further amplified in situations of stress to the respiratory system, such as exercise or exacerbations.

Over decades, it has been noted that the concept of COPD primarily focused on the progressive decline in forced expiratory volume in the first second (FEV_1) is simplistic, as it does not adequately reflect the entire pathological spectrum caused by the disease[4,5]. At the same time, LH has been shown to markedly influence patients' perceived symptoms, exercise tolerance, comorbidities or even disease prognosis. Therefore, it has become a new therapeutic target for pharmacological and non-pharmacological interventions in COPD. The aim of this review is to provide a cohesive, critical view of both the pathophysiological and clinical repercussions of LH in COPD, as well as the therapeutic options that are currently available.

DEFINITIONS AND EVALUATION PROCEDURES

Functional residual capacity (FRC) represents the lung volume at the end of tidal expiration[6]. Therefore, the diagnosis of static hyperinflation requires the demonstration that FRC, determined by plethysmography, is greater than its upper limit of normal (ULN)[7]. Its evaluation by dilution procedures is not recommended as they underestimate the lung volumes proportionally to the severity of the airflow limitation[8]. Due to the inverse relationship between body mass and FRC in patients with COPD, its evaluation is also not recommended with reference equations that include weight or body surface area[9,10].

In addition to the FRC, an increase of the residual volume (RV) or the RV/total lung capacity (TLC) ratio above the ULN may also suggest the presence of LH[11]. On the other hand, as the inspiratory capacity (IC) is a mirror image of the FRC, a reduction in the IC/TLC ratio also indicates static hyperinflation, which is an independent predictor of all-cause mortality in patients with COPD[12]. Although the available information is still limited, LH prevalence in COPD patients reaches 20 to 41%[12,13], increasing in patients with frequent exacerbations or severe airflow limitation[14].

Dynamic hyperinflation is defined by the increase in lung volume at the end of tidal expiration during exercise or other situations of increased ventilatory demands. Therefore, its diagnosis requires demonstrating that the end-expiratory lung volume (EELV), analogous to FRC under conditions of active expiration, is higher than its baseline value[15]. The

most common procedure to determine changes in the EELV is to measure the IC during exercise and subtract that value from the TLC, assuming that the latter does not change during exercise[16].

Although portable systems for measuring IC have been developed[17], its assessment during exercise requires specific equipment; thus, it is expensive and accessibility is limited. As an alternative, the induction of tachypnoea has been proposed with the use of a metronome, taking IC measurements before and after hyperventilation[18,19]. It has also been proposed to consider the relationship between the peak tidal volume (VTpeak) and the baseline TLC, since this would avoid performing IC manoeuvres during exercise[20].

IMPLIATIONS IN RESPIRATORY PATHOPHYSIOLOGY

The increase in FRC has a very variable impact on the function of the respiratory muscles, ranging from slight diaphragm dysfunction to hypercapnic respiratory failure. Static hyperinflation places the patient with COPD in a higher position of the pressure-volume curve of the respiratory system (Fig. 1), which helps to attenuate the EFL and reduces airways resistance, potentially improving the distribution of the ventilation and even the ventilation-perfusion ratio and gas exchange[21,22]. However, the increase in FRC places the inspiratory muscles in a more inefficient portion of their length-tension relationship, compromising their ability to generate force[23,24], which surely has more impact on the diaphragm than on accessory muscles[25,26]. When the FRC exceeds 55% of the vital capacity (VC), the inspiratory muscles must work not only against the elastic recoil of the lungs, but also against the inward elastic recoil of the chest wall[27]. In short, static hyperinflation increases the elastic load of the inspiratory muscles while reducing their ability to generate force.

This situation is partially compensated by diaphragm shortening, due to the sarcomere loss and the shortening of diaphragm sarcomeres[28]. Diaphragm shortening shifts the length-tension curve to the left, increasing its capacity to generate force at high lung volumes[29]. In addition, alterations in muscle fibre composition and mitochondrial concentration occur, increasing the resistance and oxidative capacity of the diaphragm[28,30-31]. All this contributes towards preserving the capacity of the overloaded diaphragm to generate force and increases its resistance to fatigue, although the capacity is not the same as in healthy subjects[29].

The development of dynamic hyperinflation limits the ability to increase IC during exercise (Fig. 2) and, therefore, generates a lower peak VT and lower peak ventilation (VE)[32]. Usually, when VT reaches 75% of the IC, a plateau occurs in the VT/VE ratio[21] in such a way that increasing the VE requires increasing the respiratory rate[32-33]. This happens earlier in patients with dynamic hyperinflation, because they have a lower IC. The tachypnoea developed to compensate for the impossibility of continuing to increase the VT worsens the functional weakness of the inspiratory muscles by forcing their contraction velocity and contributes to decreasing the dynamic compliance of the lungs[21,34-35]. In more extreme situations, it can lead to an increase

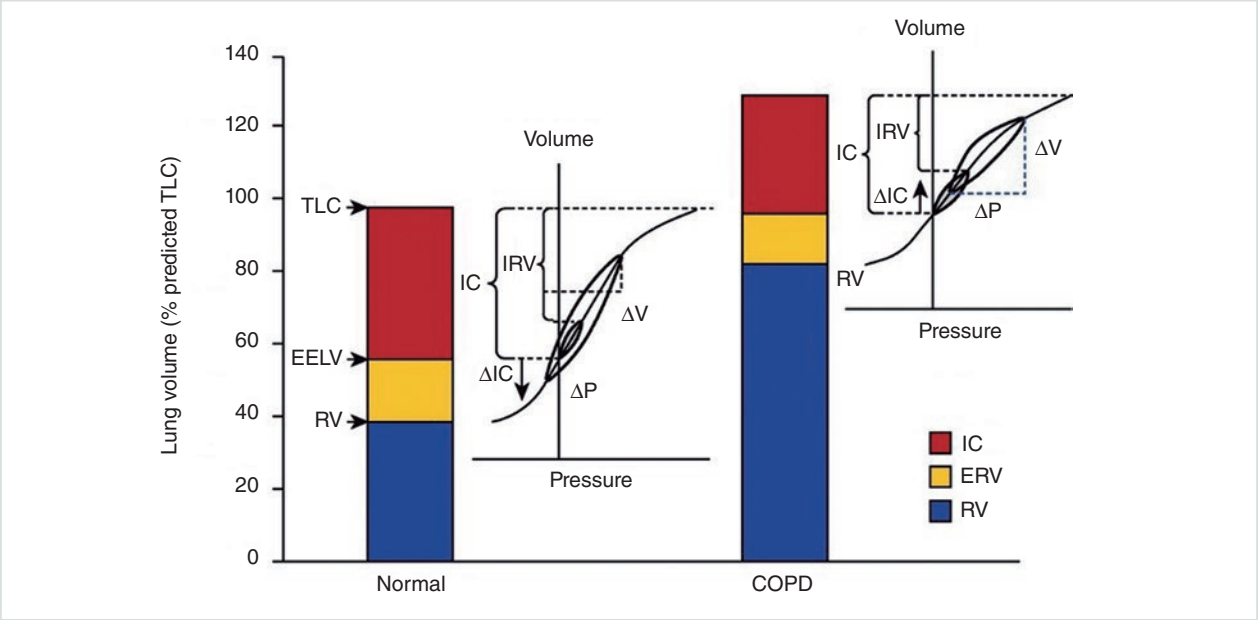

Figure 1. Schematic representation of static lung volumes and pressure-volume curves in normal subjects and COPD patients with lung hyperinflation *(reproduced from O'Donnell DE[152] with permission of the American Thoracic Society, © 2019 American Thoracic Sociey).* COPD: chronic obstructive pulmonary disease; EELV: end-expiratory lung volume; ERV: expiratory reserve volume; IC: inspiratory capacity; IRV: inspiratory reserve volume; PV: pressure-volume; RV: residual volume; TLC: total lung capacity; ΔIC: change in IC from rest to exercise; ΔP: change in pleural pressure during a tidal breath during exercise; ΔV: change in volume during a tidal breath during exercise.

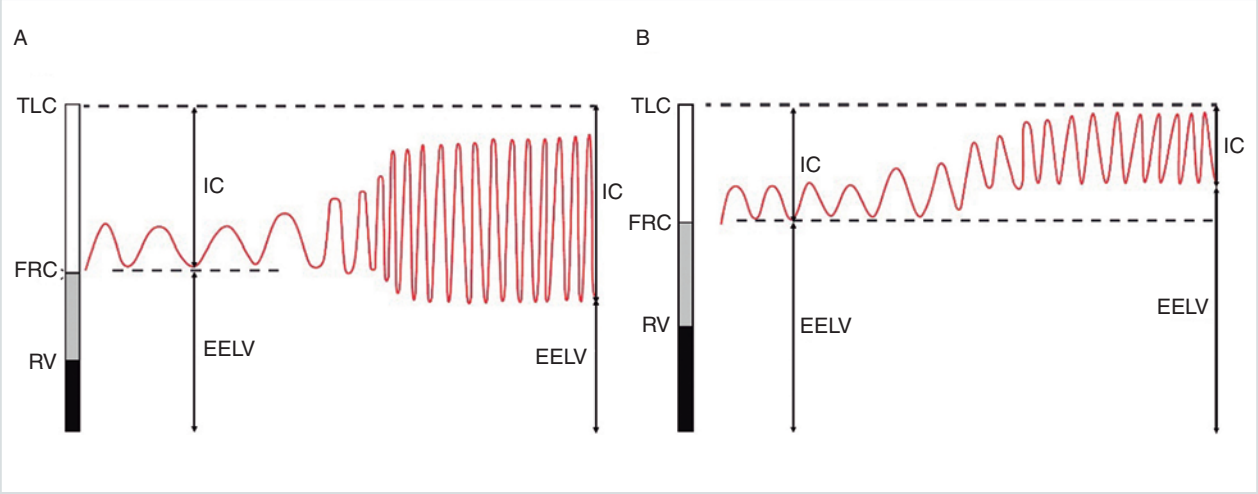

Figure 2. Changes in lung volumes during exercise (A) in healthy subjects and (B) in patients with chronic obstructive pulmonary disease and dynamic hyperinflation.
EELV: end-expiratory lung volume; FRC: functional residual capacity; IC: inspiratory capacity; RV: residual volume; TLC: total lung capacity.

in the physiological dead space and compromise the efficiency of carbon dioxide (CO_2) elimination[36]. In addition, the point at which the disproportionate increase in respiratory rate occurs to compensate for the impossibility to continue increasing the VT indicates the beginning of the imbalance between the increased central neural drive and the mechanical response of the respiratory system[22]. As dynamic hyperinflation progresses, the VT plateau occurs earlier and, therefore, this neuromechanical dissociation arises at lower work/ventilation loads[37,38].

Dynamic hyperinflation also increases the elastic and threshold load on the inspiratory muscles, thereby decreasing their efficiency by requiring more work and oxygen cost to maintain breathing[39]. In addition, the adaptation that occurs during static hyperinflation cannot compensate for the sudden workload caused by hyperventilation induced by exercise[40]. As a consequence, the mechanical disadvantage of hyperinflation and the increase in shortening velocity caused by the tachypnoea during exercise determine a functional weakness of the inspiratory muscles[39]. This higher load-capacity ratio does not allow the increased VE to be maintained for a long period of time. In turn, the increased oxygen cost of breathing and the reduced efficiency of the inspiratory muscles may predispose patients with very severe COPD to developing fatigue during exercise[27].

CLINICAL IMPLICATIONS

In patients with COPD, LH is an independent risk factor for all-cause mortality[12,41] and it has also been proposed as a risk factor for the development of exacerbations[42]. Although during a severe exacerbation there is worsened static hyperinflation, with an average decrease in IC of 280 mL or 16%[43], the relationship could be bidirectional. In fact, static hyperinflation and gas trapping (evaluated by the RV/TLC ratio) discriminate exacerbators from non-exacerbators with COPD better than FEV_1[44]. A follow-up study of patients from the Korean Obstructive Lung disease (KOLD) cohort for 61 months has shown that the presence of static hyperinflation independently increases the risk of a first exacerbation, as well as increasing mortality[41].

Dyspnoea

Patients with COPD frequently describe exercise dyspnoea as a feeling of unsatisfactory inspiration, using the descriptor "I can't take a deep breath"[34]. This difficulty to increase inspiration during exercise is perceived as unpleasant, alerts that ventilation cannot be maintained and triggers an abrupt modification in behaviour. In patients who develop dynamic hyperinflation, dyspnoea seems to depend precisely on the limitation to expand VT during exercise[45]. Therefore, it has been suggested that dynamic hyperinflation increases the intensity of dyspnoea, generating a greater neuromechanical uncoupling of the respiratory system[22]. In fact, when the VT/IC ratio (which represents the balance between the relative respiratory muscle effort and volume displacement) exceeds 70%, the intensity of dyspnoea experiences a very sudden increase[21,34].

However, this initial alteration involves different pathways in the generation of dyspnoea (Fig. 3). The lower expansion of VT and IC

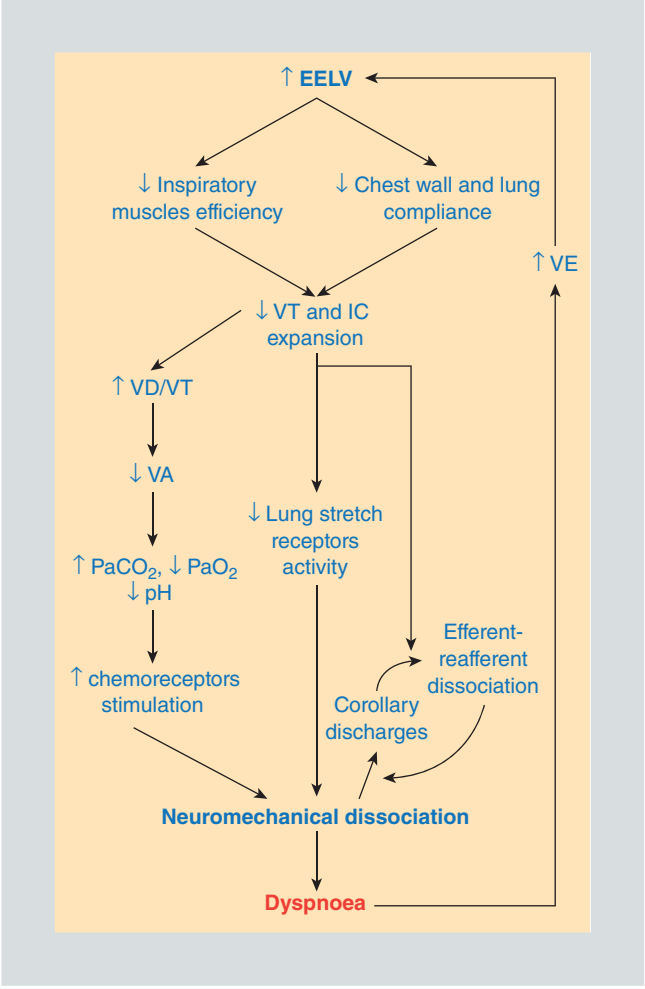

Figure 3. Potential mechanisms of dyspnoea in dynamic hyperinflation.
EELV: end-expiratory lung volume; IC: inspiratory capacity; $PaCO_2$: carbon dioxide arterial pressure; PaO_2: oxygen arterial pressure; VA: alveolar ventilation; VD/VT: ratio of physiologic dead space over tidal volume; VE: minute ventilation; VT: tidal volume.

during exercise, as a consequence of the inefficiency of the inspiratory muscles and the lower distensibility of the lungs and rib cage, decreases the stimulation of the pulmonary stretch receptors, showing that the mechanical response of the respiratory system is less than expected. In turn, this neuromechanical uncoupling induces corollary discharges from the motor cortex to the inspiratory muscles in an effort to increase tidal volume, which are also left unanswered, resulting in significant efferent-reafferent dissociation. Simultaneously, the decrease in tidal volume and increase in dead space may contribute to hypoxaemia, hypercapnia, and acidosis, causing activation of the respiratory centre via the stimulation of chemoreceptors[46].

Exercise tolerance

Due to their close relationship with dyspnoea, both static[32] and dynamic hyperinflation[27,47] reduce the exercise tolerance of COPD patients. Together with the limitation of airflow, the degree of static hyperinflation is directly and proportionally related with the annual deterioration of peak oxygen uptake (VO_2) experienced by patients with COPD[48,49]. When exercise tolerance is assessed by the distance walked in six minutes (6MWD), similar results are obtained. In 342 clinically stable COPD patients from the Phenotype Characterisation and Course of Chronic Obstructive Pulmonary Disease (PAC-COPD) study, the annual rate of change in the 6MWD was independently associated with IC/TLC[13]. Another longitudinal study also confirmed that the IC/TLC ratio is related to the annual decrease in the 6MWD, obtaining that for every 0.1 unit decrease in baseline IC/TLC ratio, the annual decline in the 6MWD distance was 13 meters[50].

Daily physical activity

In addition to the functional capacity of a patient, it is obvious that the physical activity that she/he can perform on a daily basis will depend on several factors, including socio-demographic and cultural characteristics, lifestyle,

environment and other clinical aspects, such as emotional factors, or the concurrence of different comorbidities[51]. In any case, and assuming the concurrence of some of the aforementioned factors, the contribution of LH is a main determinant of the sedentary lifestyle of patients with COPD. In a cohort of 110 patients with COPD who presented moderate-to-very severe airflow limitation and whose daily physical activity was evaluated by means of an accelerometer, it was proven that dynamic hyperinflation justified some 84% of the variability in their daily physical activity[52].

Cardiovascular function

The link between LH and reduced cardiac function has received much attention in recent years. The initial comparison of patients with severe emphysema and healthy volunteers has shown that the former had lower left ventricle (LV) and right ventricle (RV) end-diastolic volume index as well as lower cardiac index and stroke volume (SV) index, with no differences in LV and RV end-systolic volumes, LV wall mass and septal curvature[53]. In a subsequent cross-sectional study on a population-based sample of smokers and non-smokers, the extent of emphysema, measured by computed tomography (CT), was inversely related to left ventricular end-diastolic volume (LVEDV), stroke volume, and cardiac output (Q_T), even in patients with mild LH and no cardiac comorbidity[54]. Likewise, Smith et al.[55] observed that the pulmonary veins were compressed in patients with emphysema and proposed that LV filling was lowered by reduced preload due to pulmonary causes.

Using direct evaluation of static hyperinflation, Watz et al.[56] described an impaired LV diastolic filling pattern and an impaired global RV function in hyperinflated patients. Interestingly, their findings also support the concept of reduced preload in patients with LH, since LV isovolumetric relaxation time (IVRT) was unaffected by the IC/TLC ratio, suggesting no connection with left ventricular distensibility. Likewise, a study of 615 COPD patients from the German COPD and SYstemic consequences-COmorbidities NETwork (COSYCONET) cohort reported that FRC correlated positively with the mitral annulus velocity and negatively with the diameter of the left atrium[57]. Thus, LH has been significantly associated with cardiac diastolic filling in patients with COPD, suggesting a decreased pre-load rather than inherently impaired myocardial relaxation itself. Nonetheless, it is not possible to rule out an effect of static hyperinflation on ventricular function, given that in COPD patients with an IC/TLC ≤ 0.25, in addition to an impaired LV diastolic filling pattern, impairment of the RV Tei-index has been described, which provides a global estimation both systolic as well as diastolic function of the RV[56].

Another relevant aspect of cardiovascular dysfunction in COPD is the reduced pulmonary microvascular blood flow. Aaron et al.[58] suggested that LH and other smoking-related pulmonary vascular changes might lead to compression of the pulmonary capillary bed. They found an association between reduced total pulmonary vascular volume and decreased LVEDV, SV and Q_T, whereas ventricular relaxation and ejection fraction were not impaired, again suggesting pulmonary causes[58].

The effect of dynamic hyperinflation on the cardiac response to exercise is less known and, in a way, comes from classical studies on the effect of exercise and voluntary hyperventilation on cardiac function[59] as well as the extrapolation of studies conducted in patients with mechanical ventilation. Potentially, the increase in EELV can cause a decrease in preload and an increase in after-load of both ventricles, in addition to increasing ventricular interdependence secondary to the effect of pulmonary stretching (Fig. 4).

In haemodynamic studies performed during submaximal exercise in patients with COPD and no heart disease, no differences were observed in the increase in Q_T related to the intensity of exercise (Q_T/VO_2) compared to healthy subjects, although a slightly smaller increase in SV was observed, which was compensated with a higher heart rate response[60,61]. However, the increase in the right ventricle ejection fraction (RVEF) during the submaximal exercise of patients with COPD correlated negatively with total pulmonary resistance, which could reflect a certain degree of hyperinflation[61]. Nonetheless, a limitation was identified for the increase in Q_T during higher intensity exercise. Vogiatzis et al.[62] demonstrated that, during an incremental exercise test, Q_T increased up to a load corresponding with 50% of peak work capacity, while at higher intensities the increase in Q_T was attenuated, even if VO_2 kept increasing. As the heart rate continued increasing to peak work rate, this finding was attributed to a fall in SV at exercise intensities above 50% of peak capacity. Moreover, the limitation to increase the SV was associated with progressive dynamic hyperinflation and the increase in expiratory abdominal muscle recruitment[62], thereby indicating that a limitation in pulmonary mechanics might impair hemodynamic responses to exercise in COPD. Along the same lines, Vassaux et al.[58] demonstrated that patients with COPD and severe static hyperinflation (IC/TLC < 25%) have a lower exercise tolerance and a lower peak oxygen pulse, which is an indirect estimation of SV. In addition, they verified that the peak oxygen pulse is independently related to the baseline IC/TLC and FEV_1, as well as body mass index (BMI) and hand-grip force[63].

So far, only one study has simultaneously evaluated the dynamic hyperinflation and cardiac response to exercise of patients with COPD, although using surrogated outcomes. In 45 patients with COPD, Tzani et al.[47] analysed the relationship between the increase in EELV and cardiac response, assessed by the increase in the oxygen pulse and the double product (DP) reserve (product of the systolic blood pressure and heart rate), observing that the increase in EELV maintains a negative relationship with both heart rates. Although interpretation must be done cautiously because they are indirect measures, the lower response of the oxygen pulse in patients with dynamic hyperinflation could be attributed to a lower preload due to a diastolic filling defect of the LV. But the lower response of the DP reserve, an indicator of the maximum performance of the LV, suggests the involvement of other mechanisms. The DP reserve reflects myocardial oxygen consumption during exercise, which depends primarily on the tension in the ventricle wall, the contractile state of the heart, and heart rate.[64] In fact, classical studies have shown that oxygen consumption by the myocardium during exercise can be reliably estimated based on the DP value.[65] Therefore, the

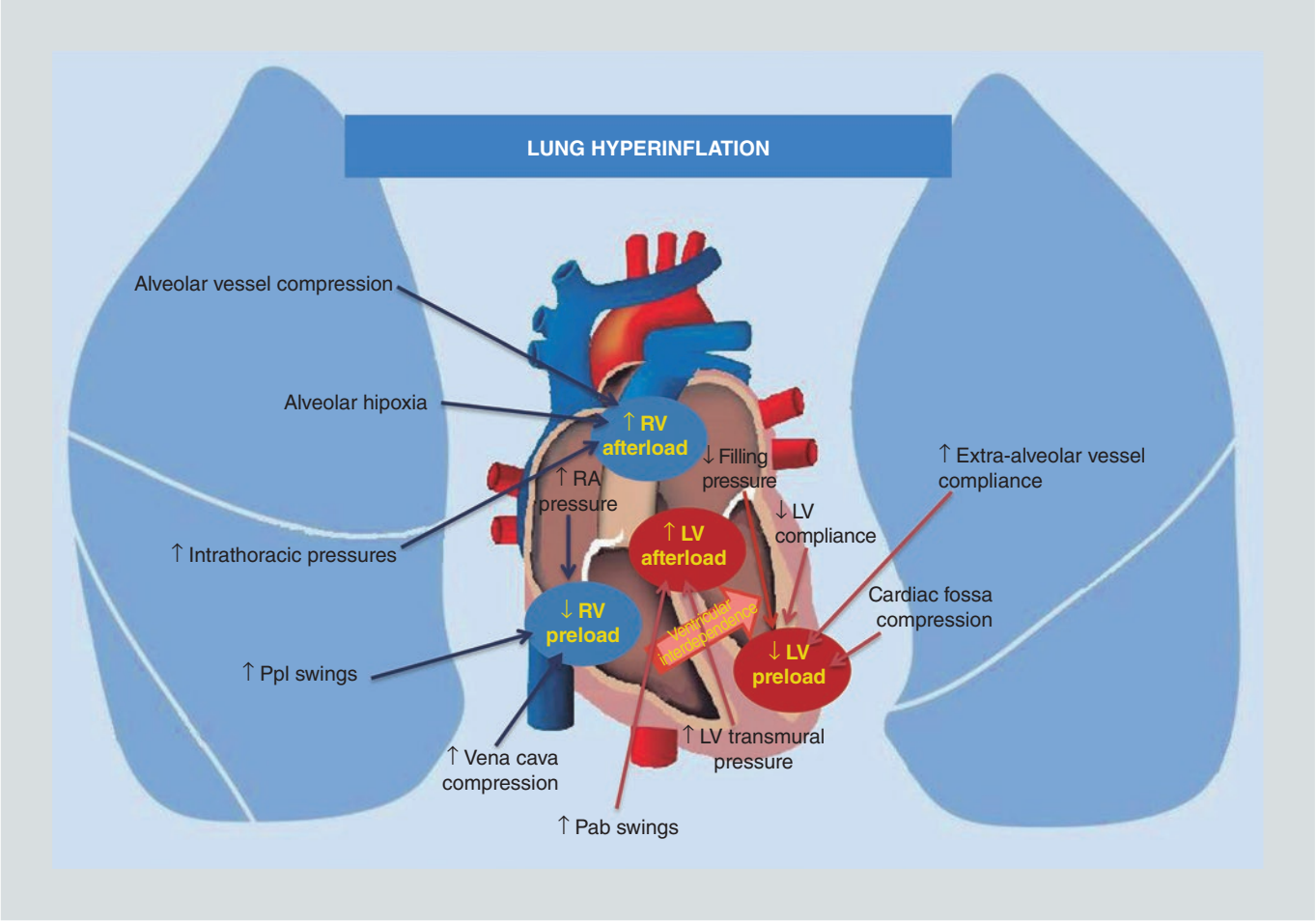

Figure 4. Potential deleterious effects of lung hyperinflation on cardiopulmonary functions during exercise in patients with chronic obstructive pulmonary disease.
LV: left ventricular; Pab: abdominal pressure; Ppl: pleural pressure; RA: right arterial; RV: right ventricular.

lower cardiac response observed in patients with COPD who develop dynamic hyperinflation may also depend on impaired LV contractility.

Finally, LH could also contribute to the elevated pulmonary arterial pressure in patients with COPD. A cross-sectional analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) COPD study has identified that the cross-sectional area of the main pulmonary artery, measured by cardiac magnetic resonance imaging, is related to residual volume, suggesting that gas trapping may contribute to pulmonary hypertension in COPD[66].

Peripheral muscle weakness

The increased work of the inspiratory muscles caused by dynamic hyperinflation could compromise the oxygen supply to the peripheral muscles[67-69], favouring their fatigue and limiting exercise capacity[70]. In fact, reducing the respiratory load of patients with dynamic hyperinflation through the inhalation of

heliox increases blood flow in peripheral muscles and reduces the intensity of leg effort, with less recruitment of type II muscle fibres, which are easily fatigued[69-71]. Overall, this results in lower leg muscle fatigue at the end of exercise[72].

Lung hyperinflation also influences the ability to generate force through the muscles of the upper extremities. In fact, it has been reported that COPD patients with severe static hyperinflation (IC/TLC < 0.25) have lower handgrip strength, and the IC/TLC ratio is an independent factor associated with the strength of upper limb muscles[73].

Lung cancer

In recent decades, it has been extensively demonstrated that COPD increases the risk of lung cancer after controlling for smoking history[74], which suggests the contribution of other factors, such as genetic or epigenetic alterations, inflammation, oxidative stress or noxious substances[75]. Furthermore, it is also known that the relationship of COPD with lung cancer is dependent on the presence of emphysema[76-79]. Recently, in a cohort of 848 COPD patients followed for an average of 4.3 years (totalling 2858 person-years), the presence of static hyperinflation was identified as an independent risk factor for lung cancer, but not for cancer of any origin[80].

Several potential pathogenic mechanisms could explain the link between LH and lung cancer. Lung hyperinflation is related to reduced elastic recoil, loss of alveolar attachments and increased airway resistance, which can favour hypoxia through ventilation-perfusion mismatching, and hypoxia has a recognised role in the development and progression of cancer[81]. Moreover, it has also been described that stable COPD patients with LH present higher airway oxidative stress, probably due to a higher production of reactive oxygen species caused by mechanical stretching of the airway epithelial cells, a reduced free-radical scavenging capacity in the airways, or a combination of both circumstances[82]. In any case, airway oxidative stress is associated with oncogenic deoxyribonucleic acid (DNA) mutation as well as cell injury, which can lead to the replication of tumour cells and the development of lung cancer in the event that cell damage is not adequately repaired[83-84]. It is also known that reactive oxygen species damage epithelial cells, induce genotoxic stress capable of DNA adduct formation[75] and increase micro-ribonucleic acid (RNA) methylation[85]. Interestingly, the FRC of patients with COPD reportedly maintains a directly proportional relationship with hypermethylation levels of microRNA-7[86], which has a well-known effect as suppressor in several types of cancer (including non-small-cell lung cancer[87]), and its reduced levels have been associated with increased tumorigenicity[88,89]. Some evidence suggests that the MicroRNA-7 (miR-7) hypermethylation found in COPD patients with hyperinflation might be related to smoking-induced up-regulation of matrix metalloproteinases as well as excessive inflammatory and oxidative stress responses[90]. Finally, it is also feasible that hyperinflation and lung cancer share a genetic pathogenic pathway independent of smoking history. For example, it has been reported that a single nucleotide polymorphism in dynein axonemal heavy chain (DNAH5) could be related to hyperinflation in COPD patients[91]. Other authors have described that the oncogenic driver

originated by the association of DNAH5 and transformer-2 protein homolog beta (TRA2B) genes might have a role in the development of squamous cell lung cancer[92].

Other comorbidities

Lung hyperinflation has also been related to the development of other comorbidities, including gastroesophageal reflux disease (GERD), a common gastrointestinal disorder associated with food reflux, acid regurgitation and chest pain as well as serious complications such as ulcerative esophagitis and oesophageal adenocarcinoma[93]. It has been shown that decreased IC is an independent risk factor of GERD symptoms in stable COPD patients[94]. The LH-induced flattening of the diaphragm as well as the increased intra-abdominal pressure and the negative intrathoracic pressure might compromise the anti-reflux barrier, forcing stomach contents through the lower oesophageal sphincter, changing the oesophagus angle with respect to the diaphragm, or by some other mechanism affecting the sphincter tone.

PHARMACOLOGICAL TREATMENT

Bronchodilators

Bronchodilators are an effective therapy for static hyperinflation, as they increase IC and inspiratory reserve volume (IRV) at rest, which is related to the lower perception of dyspnoea and greater tolerance to exercise[22]. The global evaluation by meta-analysis of localised clinical trials comparing the effect of a bronchodilator or in combination versus a placebo for at least one week in patients with COPD and LH[22,95-115] confirms an increase in IC of 0.16 L (95% confidence interval [CI]: 0.14-0.18 L)[116]. This effect is maintained in the long term, even after four years of treatment[95]. As a result, the administration of bronchodilators reduces the severity of dyspnoea and increases tolerance to exercise in the long term[114].

By increasing resting IRV and reducing EELV, bronchodilators also allow for a greater increase in VT during exercise, delaying the mechanical limitation point for its expansion. In addition, they facilitate breathing at lower lung volumes, which places the patient in a more linear portion of the pressure-volume curve of the respiratory system, delaying neuromechanical uncoupling and attenuating dyspnoea[16,22]. To date, 22 clinical trials have been identified that evaluate the effect of at least one week of bronchodilator treatment on lung volumes during exercise in patients with COPD versus placebo[22,96-98,100-115,117,118]. These are 14 parallel and 8 crossover studies, twelve of which have evaluated the effect of long-acting muscarinic agonists (LAMA), another nine long-acting beta-adrenergic agonists (LABA) and five combined LAMA/LABA. The joint evaluation by meta-analysis demonstrates their effectiveness in reducing dynamic hyperinflation, decreasing IC at isotime by 0.18 L (0.13-0.23) in the case of LAMA, 0.19 L (0.15-0.23) in LABA and 0.19 L (0.16- 0.23) when LAMA/LABA were used in combination (Fig. 5-A).

The effect of bronchodilators on dynamic hyperinflation is not exclusive to patients with severe disease. When the effect of eight weeks of dual bronchodilator therapy on dynamic hyperinflation induced by a metronome was

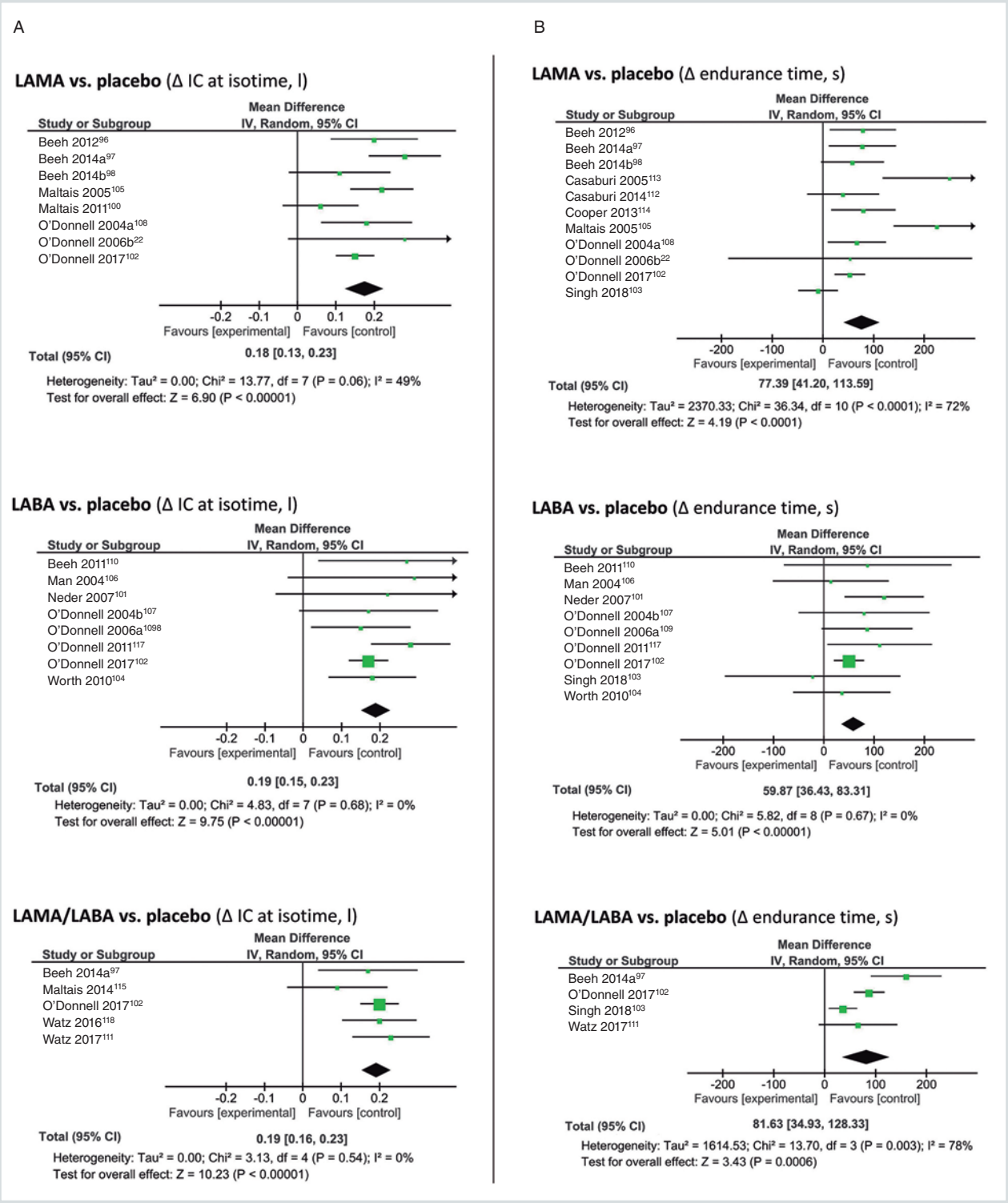

Figure 5. Forest plot of comparison of bronchodilators versus placebo effect on inspiratory capacity at isotime (A) and endurance time (B). ΔIC at isotime: inspiratory capacity decrease at isotime, defined as the highest equivalent exercise time achieved during each of the constant-load tests performed by a given subject; Δ endurance time: increase of endurance time to exhaustion during constant-load tests; CI: confidence interval; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist.

assessed in patients with mild-to-moderate COPD, an increase was detected in IC at isotime of 0.11-0.13 L versus placebo[119]. The bronchodilator-induced IC increase during exercise determines an overall increase in VT at isotime of 0.10 L (0.04-0.15), which is significantly higher than with placebo. In addition, it reduces the severity of exercise dyspnoea, showing a decrease in the Borg scale score at isotime of 0.41 (0.27-0.56) units[116]. Finally, a greater exercise tolerance is generated, which is demonstrated by an increase in endurance time, both with LAMA, LABA or dual bronchodilation (Fig. 5-B).

In addition to the effect on lung volumes in patients with COPD and LH, several clinical trials have evaluated the impact on cardiovascular function. Santus et al.[120] were the first group to examine the effects of single-bronchodilator-mediated deflation on cardiac function. They found that bronchodilators improve RV compliance indices and reduce heart rate, in association with a decrease of the residual volume. In another clinical trial, Stone et al.[121] evaluated the effect of lung deflation induced by a LABA on cardiovascular structure and function using cardiac magnetic resonance. They reported a significant improvement in biventricular SV, left atrial function, and pulsatility within the pulmonary circulation, although the bronchodilator did not improve the ejection fractions of the ventricles. To assess the effect of dual bronchodilation, COPD patients with LH were randomised to indacaterol plus glycopyrronium for 14 days[99]. It was observed that, in addition to reducing FRC and RV as well as increasing IC and the IC/TLC ratio, the dual bronchodilator therapy improved diastolic function to a greater degree than monotherapy, even though the ejection fractions did not change in both ventricles[99].

Recently, the effect of lung deflation with indacaterol/glycopyrronium versus placebo has been assessed on pulmonary microvascular blood flow (PMBF) and regional pulmonary ventilation in hyperinflated patients with COPD and no relevant cardiac abnormalities[122]. Magnetic resonance imaging showed significant improvements in total PMBF and regional PMBF in response to dual bronchodilation versus placebo. This improvement in pulmonary vasculature was significantly linked to the increased LVEDV and could therefore be mediated by a greater regional ventilation, leading to reduced parenchymal hypoxia, improved endothelial function and vasodilatation of the pulmonary vasculature[122].

Inhaled corticosteroids

Their usefulness to treat LH has been examined in few clinical trials. It has been reported that the association of fluticasone propionate with salmeterol does not potentiate its effect on dynamic hyperinflation[109], while budesonide added to formoterol significantly increases the endurance time compared to isolated monotherapy[104]. The administration of inhaled corticosteroids in extra-fine particles also has a potential effect, since the association of budesonide in extra-fine particles and formoterol in hyperinflated patients with COPD has achieved a greater reduction in RV and dyspnoea than the combination of salmeterol/fluticasone[123]. It is unknown whether this may be due to the action

of ultrafine particle corticosteroids on the small airway.

NON-PHARMACOLOGICAL TREATMENT

Volume reduction surgery

This surgical approach increases the elastic recoil of the lung, which reduces hyperinflation and facilitates the function of the respiratory muscles[124]. In selected patients, it improves static lung volumes, respiratory muscle function, exercise dyspnoea and exercise tolerance[124]. It also has an effect on dynamic hyperinflation, getting patients to adopt a slower and deeper respiratory pattern. Thus, in a series of 42 patients with emphysema predominantly in the upper lobes who underwent volume reduction surgery, a reduced EELV/TLC ratio was observed with an increased IRV; these changes remained 36 months after surgery and were associated with an improvement in the 6MWD and the maximum load reached in a progressive exercise test[125]. In patients with severe COPD, volume reduction surgery also increases the dimensions and filling of the LV and improves the wedge pressure in the pulmonary artery, in addition to improving the cardiac index, SV index and stroke work index[126].

Endoscopic volume reduction

In patients with heterogeneous emphysema and poor collateral ventilation or lack thereof in the treated lobe, the implantation of endobronchial valves has a limited effect on short-term lung volumes. Three months after the implantation of Zephir valves in dyspnoeic patients, with limitation to exercise, severe airflow limitation and an RV > 150%, the improvement in FEV_1 achieved was less than 6%[127]. However, six months after the implantation of the valves, a reduction in the RV of 700 mL was achieved as well as an increase in the 6MWD of 78 meters and an improvement in quality of life evaluated by the St George Respiratory Questionnaire (SGRQ) of 6.5 units, although 29% of cases presented pneumothorax[128]. The improvement in these outcomes was sustained during 12 months after valve placement, although 25% of treated patients presented pneumothorax in this period[129].

Endobronchial coils compress emphysematous lung tissue and may improve lung function, exercise tolerance and symptoms in patients with emphysema and severe LH. Most clinical trials show a striking effect on health-related quality of life, which reaches 8.4 units of the SGRQ in three months[130], and a more discrete effect on lung function. In a European multicentre study, the improvement in the 12-month SGRQ was 11.1 units, while the 6MWD increased by 51 meters, the FEV_1 by 110 mL and the RV by 710 mL[131]. These results have been confirmed by other studies[132-133]. The most numerous included 315 patients with emphysema and severe gas trapping, who were randomised to conventional care or usual care plus bilateral coil treatment involving two sequential procedures four months apart in which 10 to 14 coils were placed by bronchoscope in a single lobe of each lung. Twelve months later, the group treated with the coils experienced slight improvements in the distance

walked (14.6 meters) and FEV_1 (7%), and much more striking improvements in the SGRQ score (8.9 units), although 20% of patients had developed pneumonia and 10% pneumothorax[133]. Endobronchial coils have also demonstrated an effect in small series of patients with severe emphysema due to alpha-1 antitrypsin deficiency, in whom a reduction was achieved in RV of 300 mL one year after implantation[134].

Pulmonary rehabilitation

Because pursed-lip breathing increases expiratory time and counterbalances the intrinsic positive end-expiratory pressure (PEEP)[6], it could be useful in patients with LH, by creating a more efficient ventilatory pattern with a lower respiratory rate and a higher VT during exercise[135]. Although some studies confirm that it reduces EELV and the pressure generated by the inspiratory muscles, reducing the sensation of dyspnea[135], other authors have reported more variable results for the reduction of dyspnoea and increased exercise tolerance[136].

Exercise training of the lower and upper limbs reduces the ventilatory needs for a certain level of exercise due to the improved function of the peripheral muscles, which is able to reduce the respiratory rate and increase VT, decreasing dyspnoea and increasing tolerance to exercise[137,138]. In addition, the increase in VT reduces dead space, so that metabolic requirements are further reduced. However, despite its effect on dyspnoea, the ability to perform activities of daily living and at the best metabolic performance during exercise, it has not been possible to demonstrate that a conventional respiratory rehabilitation program reduces the increase in EELV during exercise[139].

Strength training of inspiratory muscles improves dyspnoea and increases exercise capacity in patients with COPD and LH[140], probably due to compensation of the muscle weakness caused by hyperinflation. In fact, this type of training has been shown to improve the strength and endurance of the inspiratory muscles[140], so it seems more effective in patients with a certain degree of inspiratory muscle dysfunction. In any case, it has been shown that inspiratory muscle training in patients with COPD reduces static hyperinflation evaluated by the IC/TLC ratio and is accompanied by clinically relevant improvement in exercise tolerance and perception of dyspnoea[141].

Inhaled gases and ventilatory support

Oxygen supplementation during constant load exercise increases endurance time and maximum exercise capacity, reducing ventilation and fatigue at isotime[142]. This is probably a result of the reduced ventilatory demand due to attenuation of the response of the peripheral chemoreceptors, which delays the appearance of the ventilatory limitation[143,144], and to the improved oxygen supply to the peripheral muscles[145].

Breathing heliox decreases airway resistance and airflow limitation, so this could also attenuate the increase in EELV during exercise[146]. It has been reported that heliox inhalation improves exercise tolerance and reduces dyspnoea in patients with COPD[147]. Improved VO_2 kinetics and increased Q have also been

reported with an acceleration of the average response time of Q and heart rate[71].

In patients with COPD and LH, non-invasive ventilation increases endurance time and reduces the perception of dyspnoea during constant load exercise[148], probably due to the better demand/capacity balance, by unloading the inspiratory muscles during exercise[149]. In general, positive pressure counteracts the intrinsic PEEP by minimizing the threshold load of the inspiratory muscles, while the pressure support reduces the elastic and resistive load of the ventilatory muscles during exercise[150]. In fact, it has been demonstrated that the application of positive expiratory pressure in patients with COPD during the six-minute walk test reduces FRC and RV, increasing the distance walked[151]. Similarly, several authors have shown that proportional assisted ventilation applied to COPD patients during constant load exercise increases the endurance time and oxygenation of the muscles of both extremities, improving dyspnoea and leg fatigue symptoms[68-72].

CONCLUSIONS

Lung hyperinflation is a frequent functional disorder in patients with COPD that is a consequence of alterations in the elastic recoil of the lung parenchyma as well as the limited expiratory flow, which can become worse in situations of stress for the respiratory system, such as exacerbations or exercise. Lung hyperinflation significantly compromises ventilatory mechanics and respiratory muscle function, which precipitate many of the perceived symptoms of patients with COPD, especially dyspnoea and exercise intolerance. It is an independent risk factor for mortality in COPD, and recent evidence supports that LH may contribute to cardiovascular dysfunction during exercise and increase the risk of lung cancer. Due to its recognised relevance, LH has been the therapeutic target of numerous clinical trials that have shown a relevant response to bronchodilators, in addition to non-pharmacological therapeutic procedures that have also demonstrated a certain degree of efficacy. Therefore, LH is undoubtedly a treatable trait of COPD (Table 1), with an exceptional clinical and prognostic relevance, which is necessary to consider in the phenotypic characterisation of patients. The information currently available does not allow for an evidence-based recommendation to be established about in which patients or how often LH should be evaluated in COPD. However, it seems possible that those with greater severity of airflow limitation, frequent exacerbations, severe dyspnoea, poor exercise tolerance or cardiovascular comorbidity present LH more frequently and may benefit from some intervention of this disorder. In such cases, the measurement of FRC, or alternatively of the IC/TLC ratio, might be systematically considered over a period of at least three years to assess its progression. The potential relationship of LH with lung cancer, gastroesophageal reflux or even sleep disturbances broadens its potential interest, but information in these fields is still very scarce.

DISCLOSURES

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Table 1. Summary table

Pathophysiological implications	– Static hyperinflation increases the elastic load of inspiratory muscles while reducing their ability to generate force. – Diaphragm shortening and alterations in muscle fibre composition and mitochondrial concentration improves diaphragm capacity to generate force and increases its resistance to fatigue. – Dynamic hyperinflation limits the ability to increase tidal volume, which requires a higher respiratory rate during exercise. – Tachypnoea worsens weakness of inspiratory muscles, increases physiological dead space and may compromise the efficiency of CO_2 elimination. – Uncoupling between the increase of inspiratory central drive and the mechanical respiratory of respiratory system has been associated with perception of dyspnoea.
Clinical consequences	– LH is an independent risk factor for all-cause mortality. – Static hyperinflation increases the exacerbation risk and discriminates between exacerbator and non-exacerbator patients better than FEV_1. – Dynamic hyperinflation increases the intensity of dyspnoea. – Longitudinal studies confirm that LH is related to annual decline in exercise tolerance. – LH is a main determinant of the sedentary lifestyle of COPD patients. – LH worsens cardiac diastolic filling in COPD patients mainly due to a decreased preload, although it is not possible to rule out an effect on ventricular function. – Dynamic hyperinflation depresses cardiac response to exercise reducing left ventricle preload and probably worsens the ventricle contractility. – LH may contribute to increase of pulmonary artery pressure. – Dynamic hyperinflation compromises the oxygen supply to peripheral muscles favouring their fatigue. – Static hyperinflation has been identified as an independent risk factor for lung cancer. – LH is related to the development of gastroesophageal reflux disease.
Treatment options	– Bronchodilators are an effective treatment for LH, increasing inspiratory capacity and exercise tolerance and reducing dyspnoea intensity. – In COPD patients with LH, bronchodilators improve some parameters of cardiovascular function. – Volume reduction surgery reduces hyperinflation and improves respiratory muscle function, exercise dyspnoea and exercise tolerance. – Endoscopic volume reduction increases quality of life with a more discrete effect on lung function. – Exercise training reduces the ventilatory needs increasing exercise tolerance. – Oxygen supplementation during exercise reduces ventilation and fatigue, improving exercise capacity.

CO_2: carbon dioxide; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in the first second; LH: lung hyperinflation.

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