Respiratory Medicine (2015) 109, 785–802

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

Mechanisms, assessment and therapeutic implications of lung hyperinflation in COPD

Andrea Rossi [a,b], Zaurbek Aisanov [c,d], Sergey Avdeev [d,e], Giuseppe Di Maria [f,g], Claudio F. Donner [h,i], José Luis Izquierdo [j,k], Nicolas Roche [l], Thomas Similowski [m,n], Henrik Watz [o], Heinrich Worth [p], Marc Miravitlles [k,q,*]

[a] Pulmonary Unit, General Hospital, University of Verona, Italy
[b] Associazione Italiana Pneumologi Ospedalieri (AIPO), Italy
[c] Clinical Physiology Department, Pulmonology Research Institute, Moscow, Russia
[d] Russian Respiratory Society (RRS), Russia
[e] Clinical Department, Pulmonology Research Institute, Moscow, Russia
[f] Department of Clinical and Molecular Bio-Medicine, University of Catania, Italy
[g] Società Italiana di Medicina Respiratoria (SIMeR), Italy
[h] Mondo Medico, Multidisciplinary and Rehabilitation Outpatient Clinic, Borgomanero (No), Italy
[i] Associazione Scientifica Interdisciplinare per lo Studio delle Malattie Respiratorie (AIMAR), Italy
[j] Pneumology Department, Hospital Universitario de Guadalajara, Universidad de Alcalá de Henares, Spain
[k] Spanish Society of Pneumology and Thoracic Surgery (SEPAR), Spain
[l] Respiratory and Intensive Care Medicine, Cochin Hospital Group, Val-de-Grâce Hospital, University Paris Descartes (EA2511), Paris, France
[m] Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologieet Réanimation Médicale (Département "R3S"), F-75013 Paris, France
[n] INSERM and UPMC, Univ Paris 06, UMR_S 1158, "Neurophysiologie Respiratoire Expérimentaleet Clinique", Paris, France
[o] Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Deutsche Gesellschaft fuer Pneumologie und Beatmungsmedizin, Germany
[p] Departments of Pneumology and Cardiology, Hospital Fürth, University Erlangen-Nürnberg, Fürth, Deutsche Gesellschaft fuer Pneumologie und Beatmungsmedizin, Deutsche Atemwegsliga, Germany
[q] Pneumology Department, Hospital Universitari Vall d'Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

Received 8 August 2014; accepted 23 March 2015
Available online 3 April 2015

* Corresponding author. Pneumology Department, Hospital Universitari Vall d'Hebron, Pg. Vall d'Hebron 119-129, 08035 Barcelona, Spain. Tel./fax: +34 93 2746083.
E-mail address: mmiravitlles@vhebron.net (M. Miravitlles).

http://dx.doi.org/10.1016/j.rmed.2015.03.010

KEYWORDS
COPD;
Lung hyperinflation;
Treatment;
Pathogenesis;
Diagnosis

Summary
The main complaint of patients with chronic obstructive pulmonary disease (COPD) is shortness of breath with exercise, that is usually progressive. The principal mechanism that explains this symptom is the development of lung hyperinflation (LH) which is defined by an increase of functional residual capacity (FRC) above predicted values. Patients with COPD may develop static LH (sLH) because of destruction of pulmonary parenchyma and loss of elastic recoil. In addition, dynamic LH (dLH) develops when patients with COPD breathe in before achieving a full exhalation and, as a consequence, air is trapped within the lungs with each further breath. Dynamic LH may also occur at rest but it becomes clinically relevant during exercise and exacerbation. Lung hyperinflation may have an impact beyond the lungs and the effects of LH on cardiovascular function have been extensively analysed.

The importance of LH makes its identification and measurement crucial. The demonstration of LH in COPD leads to the adoption of strategies to minimise its impact on the daily activities of patients. Several strategies reduce the impact of LH; the use of long-acting bronchodilators has been shown to reduce LH and improve exercise capacity. Non pharmacologic interventions have also been demonstrated to be useful. This article describes the pathophysiology of LH, its impact on the lungs and beyond and reviews the strategies that improve LH in COPD.

Contents

Introduction

Chronic obstructive pulmonary disease (COPD) is estimated to affect 10% of the population aged 40 years or more [1]. It represents a great burden to individuals and society in terms of medical expenses, mortality and disability [2]. The main characteristic of COPD is the inability of patients to cope with their daily life activities because they are limited by shortness of breath. The mechanisms underlying limitations in activity and dyspnoea are complex, but the development of lung hyperinflation (LH) plays a central role in the pathophysiology of dyspnoea and poor exercise tolerance in patients with COPD [3]. LH has a static component, which is the consequence of destruction of pulmonary parenchyma and loss of lung elastic recoil, and a dynamic component, which occurs when patients with COPD breathe in before achieving a full exhalation. The major consequence of LH is the association of the increased ventilatory workload and the decreased inspiratory muscle pressure generating capacity, despite some compensatory mechanisms [4].

Lung hyperinflation may have an impact beyond the lungs. It has the potential for significant adverse effects on cardiovascular function [5,6]. Therefore, assessment of the presence and severity of LH is a useful clinical approach to assess the impact of therapeutic interventions on symptoms, exercise tolerance and health-related quality of life.

Due to the relevance of LH in COPD, representatives of scientific societies from five European countries have developed this document covering crucial aspects of mechanisms, diagnosis and management. The aim of this document is to highlight the key aspects of this important concept and help practising physicians to understand the principles and practice of LH treatment in COPD.

Definitions and pathophysiology

The Functional Residual Capacity (FRC), which is the expression of LH, is defined as the volume of gas in the lungs and airways at the end of a tidal expiration [7,8]. Under normal circumstances, the elastic energy stored in the respiratory system during the preceding inspiration is sufficient to fully breathe out the inspired gas. Hence, FRC is determined by the opposing elastic forces of the lungs (inward) and the chest wall (outward), such that it corresponds to the static equilibrium volume of the total respiratory system. This "relaxed FRC" has also been termed V_r (relaxation volume) [9]. At V_r, alveolar pressure is equal to atmospheric pressure.

Lung hyperinflation is defined by an abnormal increase of the amount of gas in the lungs and airways at the end of the tidal (spontaneous) expiration, establishing FRC above the upper 95th percentile of the predicted values [9–11].

Conventionally, LH is at times defined as an increase in total lung capacity (TLC) $>$ 120% of the predicted value regardless of the underlying mechanisms [12]. We believe that this definition should be avoided and FRC should be used. However, we agree that in the absence of any consensus definition, the volume compartment referred to (i.e. TLC or FRC) and the method used for measurement should be specified [12]. It might also be useful to specify FRC_{He} when using the He-dilution technique or FRC_{pleth} when the plethysmographic technique is used [11].

According to the underlying mechanisms, LH is classified as "static" or "dynamic".

Static lung hyperinflation

Static lung hyperinflation (sLH) is determined by a modification of the elastic properties of the respiratory system due to a decrease of the inward elastic recoil of the lungs without changes of the elastic properties of the chest wall [8]. The most common cause of sLH is, by far, pulmonary emphysema, a disease characterized by destruction of lung parenchyma in both the panlobular and centrolobular types. The reduction of elastic fibres leads to displacement of the volume–pressure curve of the lungs leftward and upward while the elastic properties of the chest wall remain basically unchanged [13]. However, in experimental animals, there is an upward shift of the volume–pressure curve of the relaxed chest-wall such that the volume of the chest wall at any given pressure is increased, but the slope of the relationship (chest wall compliance) remains unchanged [13,14]. Hence, the static/elastic equilibrium point of the total respiratory system is moved at a higher than normal lung volume and FRC is permanently increased. Of note, the increased FRC still corresponds to the modified static equilibrium of the respiratory system (FRC $= V_r$), and alveolar pressure is equal to atmospheric pressure.

Residual volume (RV) is also increased in emphysema/COPD because of premature closure of the small airways in the dependent lung regions, a feature otherwise known as *"gas/air trapping"* [9,15,16]. This occurs early in COPD as a result of a combination of small airways closure and extreme expiratory flow limitation at low lung volume. The increase in TLC, in part, from the loss of lung recoil and, in part, from the increase in RV. With the progression of the disease, the rise in RV becomes greater than the increase in TLC (higher RV/TLC ratio), leading to a fall in VC and an ensuing FEV_1 fall [15].

Dynamic lung hyperinflation

Dynamic lung hyperinflation (dLH) is defined as an increase of FRC above the relaxed respiratory volume (V_r) because of dynamic forces [8,17–21]. In synthesis, dLH results from the discrepancy between the (a) volume to exhale, and (b) the time needed for a complete exhalation to V_r, and (c) the expiratory time constant of the respiratory system, on one hand, and the time actually available between two consecutive inspiratory efforts, on the other hand.

The distinction between sLH and dLH is important because the two phenomena have different clinical consequences and therapeutic implications. For example, dLH is tightly linked to dyspnoea and exercise tolerance while sLH is not. To avoid misleading terminology, in the present document, we use V_r to define the static equilibrium volume of the respiratory system and FRC to identify the volume at the end of a tidal expiration. With sLH, FRC $= V_r$, while with dLH, FRC $> V_r$. It should be mentioned that sLH should not be confused with "resting FRC". In fact, FRC may also vary with changes in the frequency of breathing in

normal subjects and slight amounts of dLH have consistently been found in COPD patients at rest (see below). The definitions of LH used in this article are summarized in Table 1.

Mechanisms leading to dynamic lung hyperinflation

While sLH is basically the consequence of the pathologic changes in the lungs, different mechanical causes determine the elevation of FRC above V_r, i.e. dLH: A) Decreased driving pressure for expiration, due to the reduced elastic recoil of the lungs. B) Increased airflow resistance, causing longer time constant(s). C) Expiratory flow limitation, that occurs because of the excessive compressibility of the small airways due to the destruction of the supporting alveolar attachments. Ventilation at higher lung volume, as a consequence of sLH, can lead to a positive intrathoracic pressure during expiration due to the inward recoil of the chest wall. This helps the pressure driving expiratory flow on one hand, but compresses the small airways on the other hand [22,23]. It is likely that the latter overwhelms the former by impairing the expiratory flow rate. D) High inspired volume during mechanical ventilation or exercise. This condition is not common in spontaneously breathing subjects (with the notable exception of exercise and anxiety-related hyperventilation), but it can occur in mechanically ventilated patients when excessive tidal volume are administered (controlled or assist-controlled ventilation) or when pressure support is too high (overassistance) [24]. It is also of note that in mechanically ventilated patients, expiration is further impaired by the airflow resistance of the endotracheal tube or the tracheal cannula. E) High frequency of breathing. This condition may occur during both spontaneous breathing (also in normal subjects) and assisted modes of mechanical ventilation. A short expiratory time (TE) can impair a complete exhalation to V_r if an abnormally long time is needed to exhale.

Dynamic LH is not uniform in all patients, so that the detection of the presence of LH can help to improve phenotypic characterization, and thereby helping to provide treatment more adapted to the patient's characteristics. It has been shown that not all COPD patients hyperinflate during exercise [25]. Most patients do, but a minority of patients contrast dLH by contracting the expiratory muscles. These patients have been defined as "non-hyperinflators" whereas "hyperinflator" refers to COPD patients, the majority of whom exhibit dLH during exercise. However, it has recently been observed that dLH occurs in moderate-to-severe COPD patients during exercise despite increased expiratory muscle activity [26].

Consequences of lung hyperinflation related to respiratory mechanics, gas exchange, and cardiopulmonary interaction

Static LH increases the workload to breathe through the increase of the elastic load at high lung volume, while it simultaneously decreases the pressure generating capacity of inspiratory muscles through the unfavourable geometric arrangement [27]. Dynamic LH further displaces ventilation at higher lung volume while setting the inspiratory threshold load and further worsening the inspiratory muscle geometrical arrangement and effectiveness. This negative synergy is a major determinant of dyspnoea and can lead to ventilatory failure. The consequences of LH are as follows: A) Increased elastic load. The volume—pressure curve of the respiratory system flattens at high lung volume, meaning that a greater effort is needed to produce a given tidal volume [22,23]. B) Inspiratory threshold load. When dLH occurs, the expiratory alveolar pressure remains positive throughout expiration until the new inspiratory effort occurs. Under these circumstances, the contracting inspiratory muscles must overcome the end-expiratory positive alveolar pressure (auto-intrinsic PEEP = PEEPi) before negative pressure can be created in the central airways to generate inspiratory flow [17—21]. PEEPi increases the energy cost of breathing, and it does so in a "wasted" manner because the energy spent by contracting the inspiratory muscles to counterbalance PEEPi does not generate inspiratory flow. A considerable amount of literature has shown that PEEPi is present at rest in patients with advanced COPD [20,21,28,29] and that it increases remarkably during exercise and exacerbation [30,31]. C) Decreased inspiratory muscles pressure generating capacity due to shortened fibres and decreased area of diaphragm apposition [24]. Furthermore, at a high volume distortion of the rib cage occurs due to the greater activity of the intercostal muscles [27]. Although cellular adaptation phenomena occur [32], the pressure generating capacity of the diaphragm remains impaired, though less than predicted [33]. At this point it is noticeable that respiratory muscle blood flow is impaired by intrinsic PEEP and dLH [34]. D) Impaired gas exchange. dLH is not a homogeneous phenomenon among lung regions [20]. Different time constants are distributed among different regions of the lungs according to the different presence of small airways and parenchymal pathologic

Table 1 Definitions of lung hyperinflation (LH).

Functional Residual Capacity (FRC). The amount of gas in the lungs and airways at the end of spontaneous expiration.
Relaxation or static equilibrium volume (*Vr*). The volume at which the elastic recoil pressure of the respiratory system is zero.
Lung Hyperinflation (LH). An increase of FRC above the upper 95th percentile of the normal predicted values.
Static lung hyperinflation (sLH). An increase of FRC above the upper 95th percentile of the normal predicted values, at a volume at which the elastic recoil pressure of the respiratory system is zero.
Dynamic lung Hyperinflation (dLH). A situation where FRC stands above *Vr* because the duration of expiration is insufficient for deflating lungs to reach *Vr* prior to the next inspiratory effort, and, as a result, the elastic recoil pressure of the respiratory system is no longer zero but becomes positive.

abnormalities and to the position, i.e. dependent vs. non-dependent lung regions [20]. This leads to ventilation—perfusion mismatching, eventually leading to hypoxemia [35—37]. CO_2 retention may also be a consequence of dLH. Briefly, the combination of increased mechanical workload with decreased inspiratory muscles pressure generating capacity determines a condition of inspiratory muscles pending fatigue, leading to rapid shallow breathing that is a very inefficient ventilatory pattern for CO2 removal, such that hypercapnia ensues and respiratory acidosis may occur [31]. E) Impaired cardiopulmonary interaction. Great negative intrathoracic pressure swings during inspiration and positive intrathoracic pressure during expiration markedly impair cardiovascular function [38]. F) Mechanical volume restriction. As a consequence of dLH, VT expands to occupy most of the IC and IRV reaches its minimal value in the face of an increasing central drive. By increasing resting IC, bronchodilators release VT restriction and delay mechanical limitations [12].

Clinical importance of lung hyperinflation

Relationship between lung hyperinflation and dyspnoea

Dyspnoea is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations [*or sensory modalities, including increased breathing work/effort, air hunger, and chest tightness*] that can vary in intensity [39]". Like pain, dyspnoea is a multidimensional symptom that combines a sensory dimension (perception of abnormal respiratory-related stimuli, or "respiratory sensations") and an affective dimension (emotion associated with the respiratory sensations) [39—41]. Depressive responses can ensue, depending on the magnitude of the dyspnoea-related alterations of lifestyle and the capacity of the dyspnoeic person to cope with these changes [39,40]. In COPD, dyspnoea is frequent, and grows in severity with disease progression. Exercise-related dyspnoea is a major driver of COPD-related impairment in quality of life, together with exacerbations [41]. Dyspnoea belongs to many COPD-relevant prognostic indexes [42—44]. In addition, the mere existence of dyspnoea has a strong negative prognostic value [45]. Schematically, dyspnoea occurs when there is an imbalance between the intensity of the neural drive to breathe and the intensity and nature of the information that the respiratory system sends back to the brain in response to the motor command [39]. In other words, if a strong mechanical load due to bronchopulmonary alterations is not overcome by an adequate respiratory muscle response, the corresponding respiratory sensations will be associated by the brain with a negative emotion (e.g. fear, anxiety, depression, frustration ...), which defines dyspnoea [39]. This is precisely what occurs during acute dLH in COPD, be it induced by exercise, an exacerbation, or any other cause of hyperventilation (like anxiety). With the rapid increase in FRC that defines dLH, the sensory traffic to the brain increases because of the increased elastic and threshold loads. This is answered by an increased motor drive, but at the same time, LH shortens the diaphragm and other respiratory muscles that become less apt to generate the pressure needed to overcome the load. This results in the neural drive versus sensory information described above, hence dyspnoea. Of note, the nature of exercise-related dyspnoea in COPD is related to the degree of exercise-induced dLH [46,47]: at the beginning of an exercise test, COPD patients mostly report an "excessive inspiratory effort" sensation; with the rapid constitution of dLH, the sensation changes to "air hunger". This occurs roughly when the inspiratory reserve volume is 0.5 L or less. This is important because "air hunger" is more strongly associated with negative emotions than "excessive work/effort" [48].

In COPD patients, dyspnoea correlates poorly with FEV_1 [49] and better with dLH [50]. Abundant literature during the last decades has related dLH to dyspnoea and has made reducing dLH a valid therapeutic target to alleviate dyspnoea. This is believed to be the main mechanism through which bronchodilators are effective in COPD-related dyspnoea. Bronchodilators likely have a predominant effect on the sensory dimension of dyspnoea and less effect on its affective dimension. However, certain interventions can alleviate COPD-related dyspnoea without obvious effects on dLH (e.g prolonged exercise time in response to the administration of opioids [51], or positive effects of rehabilitation on dyspnoea [52]). These effects might be mediated by a modulation of the affective dimension of dyspnoea.

Relationship between lung hyperinflation and exercise

As a key physiological hallmark of COPD, dLH significantly contributes to exertional dyspnoea and exercise limitation [53,54]. The combination of greater tidal volume and shorter time to exhale leads to dLH, which cannot be definitely predicted by the severity of baseline FEV_1 impairment [55]. In fact, under any condition of increased ventilation in flow-limited patients, inspiratory volume increases because of the greater central stimulation while the available expiratory time decreases because of the higher ventilatory frequency. Physiologically, initial sLH in severe COPD patients may suppress the development of dLH. In these terms, exertional dyspnoea requires further diagnostic testing [25]. It has been shown that dLH may occur even in subjects with symptomatic GOLD I COPD [56,57]. This is not surprising in view of the well known pathologic changes in the small airways preceding clinically overt spirometric impairment [15]. Nevertheless, in established COPD, dLH displaces ventilation on the upper flat portion of the VP relationship of the respiratory system such that the end-inspiratory tidal volume approaches TLC thereby inhibiting any further increase in ventilation, unless the breathing frequency is further increased. This, in turn, worsens dLH leading to rapid shallow breathing and pending CO_2 retention, as occurs in acute on chronic respiratory failure. Stable COPD patients, stop exercise when dLH pushes the end-inspiratory volume too close to TLC [12,53].

In order to diagnose dLH two basic methodologies can be used: A) Serial measurements of IC to detect its changes,

assuming stability of total lung capacity (TLC), and considering decreased IC as a reciprocal surrogate marker of increased FRC [17,58,59]. Contrarily to the ability of healthy subjects to completely exhale elevated tidal volumes by recruiting expiratory muscles and increasing expiratory flow, patients with COPD cannot overcome expiratory flow limitation (EFL) to complete exhaling the elevated tidal volume. Consequently, this leads to a decrease in IC followed by an elevation of FRC during exercise [60]. These measurements are directly dependent on the accuracy of IC assessment during rest and exercise. Today, there are no conventional recommendations for performing IC manoeuvers during exercise, data analysis and interpretation, however useful practical suggestions can be found elsewhere [59]. B) Exercise and maximal flow-volume loops comparison methodology is based on matching of the maximal flow-volume loop (MFVL) and the tidal flow-volume loop during exercise (extFVL) at different work intensities [61,62].

Interestingly, despite having greater metabolic and ventilatory requirements, obese COPD patients do not experience greater dyspnoea and exercise limitation than normal-weight COPD patients with comparable airway obstruction. This, partly, reflects the mechanical advantage of breathing at relatively lower lung volumes in obesity, as demonstrated by Ora et al. [63].

Relationship between lung hyperinflation and exacerbations

The definition of exacerbation is based on acute respiratory symptoms. However, a few studies support the conclusion that a worsening in symptoms is somehow associated with some worsening in lung function. Seemugal et al. [64] reported data from a cohort of COPD patients who had received a diary card and a peak flow meter; a minority of these patients also received a hand-held spirometer for measurement of FEV_1 and FVC. PEF fell rapidly at the beginning of the exacerbation and recovered slowly during the following month; FEV_1 and FVC also deteriorated with the worsening of symptoms and recovered slowly afterwards. Parker et al. [65] studied a small group of COPD patients referred to a tertiary care hospital because of an exacerbation. Spirometry, lung volumes, airway resistance (Raw), carbon monoxide diffusing capacity (DLCO), and metabolic variables were measured at the onset of symptom worsening, and after 14, 30, and 60 days. It was found that an exacerbation of COPD, not associated with respiratory failure, was characterized by worsening of airflow obstruction and LH, but with little change in ventilation and metabolic parameters. After 60 days, VC and IC improved on average by 17% and 18%, respectively, without changes in TLC, indicating a decrease in LH. These lung function changes were associated with a clinical improvement of dyspnoea, and show that frequent measurements of IC are feasible and useful in COPD patients admitted to hospital for an exacerbation and are more relevant than TLC measurements. Stevenson et al. [66] reported similar results in a small group of COPD patients hospitalized because of an exacerbation of COPD without respiratory acidosis. With the resolution of the acute episode, the consistent reduction in dyspnoea was associated with a significant improvement in FEV_1, FVC and IC already at discharge with a further increase after 42 days. IC increased, on average 0.23 L and 0.42 L after discharge and 42 days, respectively, reflecting a parallel reduction in FRC.

Evidence of dLH has been consistently reported in patients with exacerbations of COPD, complicated with acute respiratory failure and respiratory acidosis, requiring admission to the ICU and mechanical ventilatory support. In the past, several measurements were performed in sedated and paralyzed COPD patients receiving controlled mechanical ventilation [67]. Using the technique described by Kimball et al. [68], the patient was disconnected from the ventilator, allowing full relaxed exhalation to V_r. Although the results were dependent not only on the pathophysiology of the underlying pathologic condition, but also on the ventilatory pattern set by the ventilator, it was consistently found that FRC was up to more than 1 L above V_r [69—71]. After the pioneering observation by Pepe and Marini [72] in three ventilator-dependent patients, it was found that a positive end-expiratory alveolar pressure, measured by an end-expiratory airway occlusion and termed intrinsic auto-PEEP (PEEPi), was systematically associated with dLH, reaching values of up to more than 10 cmH_2O [69—72]. Clearly, the amount of FRC above V_r depends upon the elastic properties of the respiratory system, i.e. stiff versus compliant. For a similar value of PEEPi, dLH is greater in a compliant system rather than in one that is stiff.

In ventilator-dependent COPD patients, PEEPi and dLH must always be suspected and their measurement should be part of the routine assessment of respiratory function. In fact, the presence of excessive dLH may explain unpredicted hemodynamic instability, poor patient-ventilator interaction, and difficult weaning. Adequate changes in both the ventilator setting and in the medical treatment may contribute to decrease dLH and PEEPi, hence improving the patient's condition and prognosis.

In summary, exacerbation of COPD is associated with deterioration in lung function in general, and with an increase of dLH in particular, in both normocapnic and hypercapnic episodes. Adequate treatment of dLH relieves dyspnoea and improves VC and IC, reflecting a reduction in VR (less air trapping) and in FRC (less LH). In patients with exacerbation and respiratory failure, treatment of dLH is needed to resume the ability of spontaneous ventilation following resolution of the acute episode [73].

Extrapulmonary consequences of lung hyperinflation

Hyperinflation, intrathoracic hypovolemia and cardiac dysfunction

Studies performed almost 30 years ago indicated a link between dLH and cardiac dysfunction in patients with COPD [74—76]. In patients with severe COPD and normal cardiac function at rest, the rise in FRC during tachypnoea was associated with an increase in right atrial pressure, mean pulmonary artery pressure, and wedge pressure, which was associated with a 10% increase of the left lateral lobe area

on lateral chest X-rays. By contrast, a change in right atrial pressure during tachypnoea in control subjects did not reflect that of the left atrium in extent or direction. The authors concluded that raised wedge pressure in COPD on exercise or tachypnoea is partly due to a rise in pressure in the cardiac fossa associated with lower lobe gas trapping [75]. Of interest, 20 years later the results of the "National Emphysema Treatment Trial" showed that lung volume reduction surgery was associated with a decrease in wedge pressure [77].

Echocardiographic studies have revealed abnormal left ventricular diastolic function in patients with severe COPD [78—80]. Funk and colleagues investigated whether left ventricular diastolic dysfunction in COPD might be the result of an increased right ventricular afterload with ventricular interdependence leading to left ventricular diastolic changes [79]. They found left ventricular diastolic dysfunction to also be present in COPD patients with normal pulmonary artery pressure, suggesting a relationship between lung function and left ventricular diastolic function independently of right ventricular pressure [79]. It is of note that the 6-min walk distance and physical activity are reduced in those patients with concomitant left ventricular dysfunction compared to COPD patients without left ventricular dysfunction [5,6,80].

Jorgensen et al. [81—83] studied a group of patients with severe emphysema before and after lung volume reduction surgery by means of echocardiography, pulmonary artery thermodilution catheter, and magnetic resonance imaging (MRI). They observed that the left ventricle in patients with severe emphysema is hypovolemic, which results in an impaired stroke volume index on hemodynamic measurements [83]. Furthermore, echocardiographic parameters of left ventricular dimensions and left ventricular diastolic filling improved after lung volume reduction surgery [81]. Finally, with MRI they were able to confirm that a reduced intrathoracic blood volume resulted in smaller end-diastolic dimensions of the right and left ventricle, which had an impact on cardiac performance [82]. The authors speculated that hyperinflated lungs in emphysema result in intrathoracic hypovolemia and a decreased biventricular preload [82]. Conversely, a small heart size was shown to be a radiological indicator of emphysema on chest-X ray in patients with COPD [84].

Recently, an epidemiological study performed in 2816 subjects from the general population evaluated the relationship between cardiac function and dimensions, as assessed by cardiac MRI, and the extent of CT-emphysema [85—87]. It was found that an increase in the extent of emphysema is associated with impaired left ventricular filling [85]. A similar relationship was observed between airflow obstruction and cardiac parameters of left ventricular filling and performance. On average, lung function of the study participants was normal and only 7% of the study participants had either self-reported COPD, emphysema, or chronic bronchitis [85]. A subsequent analysis of this study revealed that the percent emphysema was inversely related to right ventricular volumes and right ventricular stroke volume [86]. Finally, a recent analysis of a small subgroup of 165 patients with confirmed COPD participating in the same study revealed that pulmonary vein dimensions were reduced compared with controls, the pulmonary vein dimensions being inversely associated with the percent emphysema [87].

Only a few studies have analysed the impact of LH on cardiac function and cardiac dimensions. Vassaux et al. [88] showed that the IC/TLC ratio is associated with lower oxygen pulse as a non-invasive surrogate of stroke volume and global cardiac function on cardiopulmonary exercise testing. Of interest, both lung volume reduction surgery and lung deflation by tiotropium demonstrated that oxygen pulse increases following interventions in patients with COPD [89,90]. Watz et al. [6] showed the relationship between LH and various preload dependent echocardiographic parameters of right and left ventricular function along with the association of LH with cardiac chamber size on echocardiography in patients with COPD. Summarizing the currently limited evidence, it is fair to conclude that LH might be one of major factors impairing cardiac function in COPD.

Hyperinflation and skeletal muscle dysfunction

Muscle dysfunction often occurs in respiratory and peripheral muscles in all stages of COPD [91,92]. Lung hyperinflation has a pivotal role in respiratory muscle dysfunction as it places the respiratory muscles at a mechanical disadvantage [92]. However, the contractile strength of the diaphragm is preserved, which seems to be the result of persistent involuntary training secondary to the increased work of breathing [92]. Consequently, the diaphragm adapts by remodelling with a relative increase of the fatigue-resistant type I muscle fibres [33,92]. Other respiratory muscles also show similar changes [92].

It seems that muscle deconditioning is the main driver of peripheral muscle dysfunction in COPD [91,92]. Accordingly, most microscopic and molecular changes of the peripheral muscles can be explained by the disuse of the locomotor muscles of the lower limbs [92]. Muscle disuse is the result of dyspnoea on exertion during daily life activities and dLH has been demonstrated to be a major contributing factor of physical inactivity in patients with COPD [93]. Therefore, even though indirectly related, it seems that LH not only has a pivotal role in respiratory muscle dysfunction but also in peripheral muscle dysfunction.

Assessment of lung hyperinflation

Lung hyperinflation can be suspected in patients with severe COPD by physical examination, though it is of limited value in mild to moderate disease. There are some methods suitable for measuring LH in clinical practice.

Physical examination

The classic sign of LH is the *barrel chest* deformity, which has long been described as a sign of "emphysema" [9]. Barrel chest refers to an increase in the anteroposterior chest diameter, but besides LH it can be linked to other factors (age, *etc.*), and in the end, the sensitivity and specificity of this sign are not satisfactory. The *Hoover sign* consists in the paradoxical inward motion of the lower

lateral rib cage during inspiration. It has been attributed to direct traction by the flattened diaphragm on the lateral rib margins. The *Hoover sign* is easy to recognize, but it has relatively high interobserver variability [94]. *Thoracoabdominal asynchrony* consists of a paradoxical inward motion of the anterior abdominal wall during inspiration, similar to that observed in patients with bilateral diaphragmatic paralysis [95]. This sign can be easily detected by simple inspection, particularly in the supine position. Some studies have suggested that thoracoabdominal asynchrony is associated with a poor short-term vital prognosis. The *use of scalene muscles* during inspiration (*respiratory pulse* or *sign of Magendie*) reflects the greater recruitment of inspiratory muscles because of a mechanical disadvantage of the diaphragm due to LH [95]. This sign is usually observed in more severe stages of COPD and is characterized by good interobserver variability. The *pursed lip breathing* is used instinctively and voluntarily by some patients with COPD in order to reduce dyspnoea [96]. Other signs for clinical detection of LH include paradoxical pulse, excavation of suprasternal and supraclavicular fossae during inspiration, jugular venous filling during expiration, reduced length of palpable trachea and tracheal descent with inspiration [97]. It should be noted that the detection of these signs is clearly dependent on the observer.

Measurement of FRC

The methods most commonly used for lung volume measurements are body plethysmography, gas dilution techniques (helium dilution method and nitrogen washout method) and imaging studies (computed tomography). However, these techniques are not interchangeable: in moderate-to-severe airflow obstruction dilution methods tend to underestimate lung volume?? and body plethysmography tends to overestimate FRC. Other techniques such as MRI, optoelectronic plethysmography, structured light plethysmography or respiratory inductance plethysmography are more suitable for research tools rather than clinical practice.

Body plethysmography is the reference technique for the measurement of lung volume. It is less time-consuming than the dilution techniques, and does not add much time to that necessary for spirometry. A crucial point is the necessity to keep the panting frequency below 1 Hz during plethysmographic measurement. The plethysmographic technique measures the thoracic gas volume (TGV), which can overestimate the true FRC in patients with severe airflow obstruction basically because of two mechanisms. One occurs when abdominal gas is compressed and decompressed in synchronic with thoracic gas, while the other mechanism is the significant pressure losses between alveoli and airway opening in the presence of obstructed airways [98].

The gas dilution methods are based on the use of a tracer gas (such as helium) that is inhaled at a defined concentration until equilibration is reached, and then measured again in expiration [99]. In normal subjects there is good agreement between measurements using the helium dilution method (FRC_{He}) and TGV. The measured volume takes into account the well-ventilated areas, such that FRC_{He}, in COPD patients it can be lower than TGV because of the effect of non-communicating airways [98]. The difference between the FRC_{He} and TGV is particularly pronounced in severe emphysema. The gas dilution methods can be used in patients who cannot get into a body plethysmograph, and in very severe (bed-ridden) or claustrophobic patients [100].

In patients who are not able to cope with the plethysmographic techniques either because of their status (exacerbation of COPD) or during exercise testing, the degree of LH can be determined by measuring the IC, which only requires a spirometer. The IC is the maximal volume of air that can be inhaled after a spontaneous expiration to FRC. Therefore, the IC is the difference between TLC and FRC. In the absence of reliable predicted values for the IC, the difference between predicted TLC and predicted FRC can be used as a predicted normal for IC. In addition, IC can be normalized for the value of TLC by means of the IC/TLC ratio. At a constant TLC, a decrease of IC represents an increase of FRC. It has been shown that TLC remains constant over short time periods and during exercise [101]. Bronchodilation studies have established that IC as a measure of hyperinflation correlates better with dyspnoea and exercise performance than FEV_1 [101,102]. The use of IC for the testing of LH has two major disadvantages: firstly it ignores the isolated increase in RV, and, on the other hand, it is assumed that patients do not change their TLC during an exacerbation or bronchodilator therapy.

Imaging techniques

Lung volumes can be obtained from conventional chest radiographs. In early studies, a good correlation was found between plethysmographic and radiographic techniques, but radiographic techniques are time-consuming, not standardized and are now mainly used for quantitative purposes only in paediatric practice [103]. The most helpful radiographic sign of LH is a flattening of the hemidiaphragms [104]. Other radiological signs of LH include an increase in the retrosternal air space (measured 3 cm below the manubrial–sternal junction) of more than 2.5 cm, an increase in lung height and a low standing of the diaphragm (the right dome of the diaphragm at or below the anterior segment of the 7th rib).

Computed tomography (CT) is an important method for assessing lung condition. Dedicated post-processing softwares allow rapid reproducible measurement of thoracic gas volume. Lung volumes determined by CT are less prone to inaccuracies related to chest wall or image distortion. TLC measured by plethysmography and CT usually has a very high correlation ($r > 0.9$), and TLC measured by plethysmography is greater than that measured by inspiratory CT (up to 1 L) [105]. The difference between plethysmographic TLC and TLC determined by CT is reportedly greatest among subjects with $FEV_1 < 30\%$ of predicted [106]. The limitations of the measurement of lung volumes by CT include difficulty with maximum inspiratory manoeuvers and breath-holding techniques during scanning. In addition, one should keep in mind that plethysmographic TLC as well as FRC_{He} are measured in the sitting position whereas CT-TLC is measured in the supine

position. Therefore, it can be predicted that plethysmographic TLC must be greater than CT-TLC [7]. This discrepancy should be even larger in obese patients.

It has been suggested that CT may help in the early diagnosis of COPD. In particular the comparison between inspiratory and expiratory images can show air trapping and help to distinguish COPD phenotypes [107] and show that small airway disease precedes emphysema [108]. Although extremely interesting and promising, this technique is probably more suited to research protocols, requiring further work to for use in clinical settings.

Measurement of pulmonary hyperinflation during mechanical ventilation

Dynamic LH and PEEPi are fundamental aspects of the pathophysiology of acute respiratory failure in patients with a severe exacerbation of COPD. Hence, assessment and measurement of dLH and PEEPi is a crucial aspect in the overall clinical management of these patients [18,20,21,67]. The amount of dLH can be measured in heavily sedated or paralysed ventilator-dependent patients by allowing a complete exhalation after disconnection from the ventilator. In this condition, PEEPi can be measured by means of the end expiratory occlusion technique [72] and/or on-line monitoring [109]. In actively breathing patients, measurement of PEEPi by means of end-expiratory occlusion is more difficult because of respiratory muscle activity [110] and may require the use of an oesophageal (and gastric) balloon [31,111,112]. This technique is more appropriate as a research tool and poorly suited to clinical practice [113]. However, the estimation of PEEPi in ventilator-dependent patients may be important to set the adequate level of PEEP or CPAP to reduce the patient's work of breathing, to prevent patient-ventilator dissynchrony, and during weaning [112,114].

Pharmacologic treatment of pulmonary hyperinflation

Bronchodilators are the main pharmacological agents targeting LH: their primary aim is to decrease the level of airflow limitation, which represents one of the leading mechanisms of exercise limiting dLH. Since airway obstruction is also related to inflammatory changes, anti-inflammatory agents could be of some value.

The beginning of the story: short-acting bronchodilators

In 1979, Ramsdell et al. [115] demonstrated that isoproterenol (short-acting beta-agonist) produced an increase in IC even in some patients with no effect on FEV_1. The authors interpreted this finding as an indication that improvement in static lung volumes can reflect bronchodilation in the absence of improved expiratory flow. Subsequently, it was shown that, in asthmatic as well as in COPD patients, dyspnoea relief following bronchodilation was correlated with changes in IC but not FEV_1 [116,117]. The improvement in FRC after salbutamol was found to be more marked in flow-limited than in non flow-limited COPD patients [118]. In COPD, reduced levels of LH were associated with improved diaphragmatic contractility, likely related to the mechanically more favourable conformation of the diaphragm. Along the same line, Dal Vecchio et al. [28] found that fenoterol improved diaphragmatic strength in COPD patients. In parallel, O'Donnell et al. reported that exertional dyspnoea and endurance time were closely related to dLH, which was reduced by a short-acting anti-muscarinic agent [119].

Short-acting bronchodilators are recommended as-needed for symptom relief in patients with COPD. For maintenance treatment of patients with moderate to very severe airflow obstruction, the arrival of long-acting bronchodilators was a significant step forward. These agents could also be useful in patients with mild airflow obstruction but significant LH during relatively low levels of exercise [58].

Long-acting beta2 adrenoreceptors (LABAs) and long-acting antimuscarinic agents (LAMAs): the story continues

The first LABAs released were formoterol and salmeterol, which both have a 12 h duration of effect. Some years later, a LAMA with 24 h duration of action, tiotropium, was marketed, followed by glycopyrronium (24 h duration of action) and aclidinium (12 h duration of action). In parallel, indacaterol, an ultra-LABA (24 h duration of action), has been made available and will be followed by several others (e.g., olodaterol, vilanterol).

All those that are already on the market have been tested regarding their effects on LH, both at rest and during exercise, as recently reviewed [120] and shown in Table 2. Figure 1 provides a typical example of the findings from these studies.

Dual bronchodilation

Several LABA + LAMA combinations are currently being developed. Some studies have shown complementary effects on lung function and some clinical endpoints as compared to mono-bronchodilation [121]. In addition, new long-acting molecules with muscarinic antagonist and beta2 agonist properties (MABAs) are also undergoing clinical testing, with the first results showing similar levels of bronchodilation as with the association of a LABA and a LAMA [122]. Only one fully published study compared dual bronchodilation (indacaterol + glycopyrronium = QVA149) to mono-bronchodilation (tiotropium) and placebo on LH and exercise tolerance in 85 patients [123]. This was a cross-over study with each treatment period lasting 21 days. QVA149 and tiotropium improved exercise endurance time by about 1 min versus placebo (baseline endurance time: about 8 min), with no difference between the two agents. As compared to tiotropium, QVA149 had greater effects on pre- and post-exercise IC as well as on trough IC, FEV_1 and FVC.

As mentioned previously, IC has spontaneous variability, possibly due to slight spontaneous changes in FRC, particularly in COPD patients, in whom a small amount of dLH has

Table 2 Summary of published studies assessing the effects of long-acting inhaled bronchodilators on hyperinflation at rest and exercise tolerance as assessed using endurance testing with measurement of endurance time, Borg dyspnoea score and inspiratory capacity (IC). Adapted from Ref. [8].

Class	Agent	Number of studies	Study duration	Sample size	Significant effect			
					Resting IC	Endurance time	Isotime	
							Borg	IC	V_t
Beta2 agonists	Formoterol	1	2 weeks	21	Y	N	N	Y	Y
	Salmeterol	2	2 weeks for both	16 & 23	Y	Y & N	N & Y	Y	Y
	Indacaterol	2	2 weeks & 3 weeks	27 & 90	Y	Y	Y	Y	—
Anticholinergics	Tiotropium	3 vs. placebo	7—10 days, 6 weeks × 2	18, 187 & 261	Y	N, Y & Y	N, Y & Y	Y	N, Y & Y
		1 vs. placebo as add-on to formoterol	2 weeks	33	N	Y	N	N	N
	Aclidinium	1	6 weeks	181	Y	Y	Y	N	Y
	Glycopyrronium	1	3 weeks	108	Y	Y	Y	Y	—

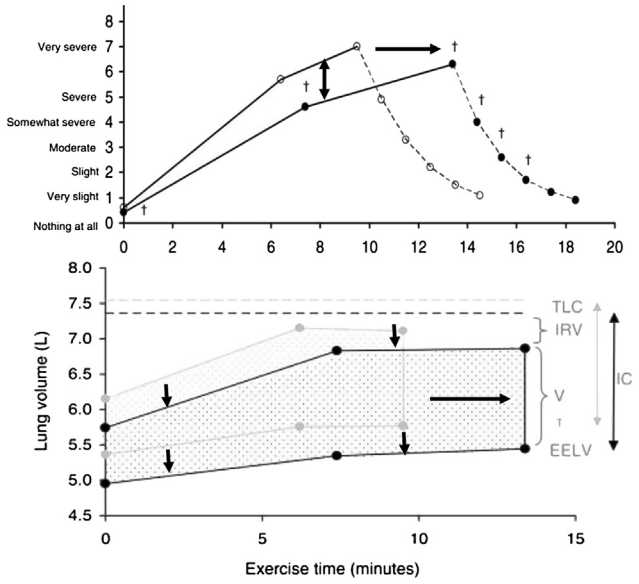

Figure 1 Typical findings from studies of the effects of a bronchodilator on exercise tolerance and hyperinflation. Subjects perform constant load endurance testing at a given percentage of maximal work capacity with serial dyspnoea assessments using the Borg scale (top panel) and spirometric measurements of mobilized lung volumes (tidal volume and inspiratory capacity manoeuvers) (bottom panel); total lung capacity (TLC) is measured by body plethysmography before exercise. IRV: inspiratory reserve volume; VT: tidal volume; EELV: end-expiratory lung volume; IC: inspiratory capacity. Horizontal arrows show the effect of the bronchodilator on endurance time. Vertical red arrows show its effects on dyspnoea (top panel) and operational lung volumes (bottom panel). EELV in the Figure corresponds to FRC in the text. From Maltais et al. Chest 2005; 128: 1168 with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

been inferred from measurement of PEEPi at rest. It has been suggested that improvements of IC $>$ 10% of the baseline value exceed the spontaneous variability of the parameter [118]. However, there is neither any report or consensus on the minimally important clinical difference (MICD) for IC, as is the case for FRV1 [124].

Anti-inflammatory agents

At least two studies have shown an effect of inhaled corticosteroids (ICS) added to LABAs on LH and exercise tolerance; one was performed with salmeterol-fluticasone (SFC), the other with formoterol-budesonide [125,126].

In both studies, the patients were randomised to receive the combination, the LABA alone or placebo. Similar results were found (although differences between SFC and salmeterol alone were not statistically tested in the corresponding study), with additional effects of the ICS on top of LABA on LH at rest and during exercise, endurance time and isotime dyspnoea ratings. These findings and the quick occurrence of ICS additional effects could relate to reciprocal modulation of the function of receptors to

corticosteroids and beta2 agonists or non-genomic effects of corticosteroids.

Some studies have specifically assessed the effects of ICS (alone or in fixed-dose combinations with LABAs) formulated as extra-fine particles, hypothesizing that reaching smaller airways might help obtaining greater effects on LH and exercise tolerance. In very small studies, it was found that beclomethasone HFA and beclomethasone-formoterol in combination in extra-fine particles decreased LH and relieved symptoms in COPD patients [127,128]. The conclusions were limited by small sample sizes, and lack of placebo control in the latter study.

Roflumilast is an oral PDE4 inhibitor indicated in addition to long-acting bronchodilators for the prevention of exacerbations in patients with severe airflow obstruction, chronic bronchitis and repeated exacerbations. In one study [129], it was shown to improve IC, SpO2 and peak ventilation slightly albeit significantly during exercise, with no effect on resting LH or endurance time.

The position of theophyllines in the guidelines relates to their low benefit-risk ratio. A small study showed that theophylline improved resting gas exchange and maximal voluntary ventilation and some indices during incremental exercise testing [130]. However, in this study as in others [131] lung volumes were not assessed during exercise. A recent pilot study assessed the effect of theophylline on top of dual inhaled bronchodilation on spirometry and exercise endurance. A trend towards a positive effect on exercise tolerance was found but with no significant change in IC [132].

Comparisons between strategies

Only a few studies have directly compared the effects of these pharmacological therapeutic "strategies" (i.e., LAMA on the one hand, FDC on the other, and their association) on LH. In the study by Santus et al. [133], the acute effect of tiotropium on resting IC (but not RV) was of greater magnitude than that of budesonide/formoterol.

In conclusion, high levels of evidence regarding the effects on LH and subsequent improvement in exercise tolerance are available for inhaled bronchodilators. Inhaled bronchodilators appear to be useful tools to relieve exertional dyspnoea and improve exercise tolerance through decreasing LH in COPD patients.

Non pharmacologic treatment of pulmonary hyperinflation

Treatments that primarily decrease the respiratory rate (f) and increase tidal volume (V_T)

These treatments are pursed-lip breathing (PLB), inspiratory muscle training (IMT), peripheral muscle training and oxygen.

The mechanisms through which PLB reduces dyspnoea are: a) decreasing Ti/Ttot, thus increasing the expiratory duration. b) counterbalance of intrinsic PEEP. PLB produces a substantial increase in V_T along with a reduced f and minute ventilation [134]. This technique increases expiratory airways pressure, reducing expiratory airway collapse, but, at the same time, impairs the rate of expiratory flow. Patients that did not instinctively adopt PLB did not assume it naturally for long periods of time even when properly taught [135]. PLB was shown to improve the rate of dyspnoea recovery to basal levels [136], and to reduce f in patients with COPD during exercise on cycle-ergometer.

IMT is a useful technique in PR, associated with whole body exercise training (ET). FRC does not change through IMT [137]. IMT might be useful when added to whole-body ET in individuals with marked inspiratory muscle weakness or those unable to cycle or walk because of comorbid conditions [138]. Exercise training lowers ventilatory demand, resulting in a lower frequency of breathing at a given level of exercise. With a longer expiratory time there is less dynamic dLH and therefore less dyspnoea [139,140]. Many studies have shown that leg training decreases f during exercise and increases IC [135,141—144]. Optimization of bronchodilator therapy before ET in patients with airflow limitation is generally routine in PR [138].

Several observations in normoxemic COPD patients have demonstrated the favourable effect of oxygen supplementation during exercise [145,146], reducing f and dyspnoea. The improvement in endurance time was correlated with a decrease in FRC [147]. In a group of 18 severe COPD patients, oxygen reduced the degree of dLH during recovery from exercise [137]. The effects of supplemental oxygen on dLH show a considerable inter-patient variability with a reduction of LH in a subset of patients, in general with greater baseline airway obstruction, greater ventilatory constraints during exercise and poorer exercise performance. Oxygen also induces dyspnoea relief due to reduced central neural drive and improved oxidative capacity of the active peripheral muscles.

The current evidence does not support the widespread use of oxygen supplementation during ET in COPD with dLH, except in patients already receiving long-term oxygen therapy [138].

Treatments that primarily reduce airflow limitation

There are two options to reduce airflow limitation: heliox and increasing elastic recoil.

Heliox (heliox/oxygen ratio 80:20) decreases turbulent flow in large airways and at branch points in the tracheobronchial tree. Exercise endurance and peak ventilation time significantly increase with heliox, with a reduction in dLH and dyspnoea at isotime, significantly correlated with the increase in IC induced by heliox [147]. The use of this technique as an adjunct in PR exercise training remains to be established [137].

The second strategy is to improve lung elastic recoil. Lung volume reduction surgery (LVRS) refers to elimination of emphysematous hyperinflated portions of the lung, which allows the remaining pulmonary parenchyma and the respiratory muscles to function more effectively. Several randomised trials have compared LVRS with optimal medical treatment providing convincing evidence that this procedure improves respiratory function, exercise capacity, and dyspnoea in selected patients with advanced emphysema to a greater extent than optimal medical therapy

[148]. By far, the largest clinical trial was the NETT [20], in which only the subset of patients with upper lobe predominant emphysema and low exercise capacity (24%) showed a significant reduction in total mortality with surgery (7% vs. 15% per year, risk ratio 0.47) [149]. Endobronchial valve placement can improve lung volumes and gas transfer in some selected COPD patients and prolong exercise time by reducing FRC [150].

Bullectomy can also contribute to reducing dLH: the most common indication for bullectomy is severe dyspnoea in the setting of a large bulla occupying at least 30—50% of the hemithorax. Another indication is a history of recurrent pneumothorax.

Treatments aimed to relieve the inspiratory threshold load

Inspiratory threshold load can be relieved by pursed-lip breathing (PLB) and positive end-expiratory pressure. The effects of PLB are summarized above.

In patients with flow limitation by dynamic airway collapse, small amounts of external PEEP or CPAP (continuous positive airway pressure) can be beneficial since intrinsic PEEP can account for about 1/3 of the total work of breathing [151]. A meta-analysis of 7 studies has shown a modest beneficial effect of ventilatory support on exercise tolerance [152]. CPAP unloads inspiratory muscles from the inspiratory threshold load imposed by intrinsic PEEP [144,151,153]. Inspiratory pressure support (IPS), a form of pressure-targeted mechanical ventilation in which each breath is patient triggered and supported has been shown to improve exercise tolerance [140,152—157] and reduce lactate production [158]. Proportional assisted ventilation (PAV) has also been shown to increase exercise tolerance [134,159]. The combination of PEEP/CPAP and IPS [160] or PAV [161] decreases the inspiratory workload in mechanically ventilated patients.

The application of low levels of CPAP (much lower than that set for obstructive sleep apnoea) during exercise can improve exercise tolerance by reducing the inspiratory threshold load without changing FRC [151]. BiPAP can decrease both the inspiratory workload and FRC thorough a modification of the breathing pattern [162].

Overview of clinical importance of lung hyperinflation

Most COPD clinical documents and guidelines currently base their recommendations on FEV_1, symptoms and exacerbations. Although the measurement of lung volumes is a relevant aspect in the functional assessment of the patient, in practice, most therapeutic decisions are only based on spirometric values.

By and large, the combination of static and dynamic LH increases as COPD worsens, but dLH occurs independently of FEV_1 values [25] during daily real life activities [54], being the main limiting factor in physical activity regardless of classification with GOLD or BODE [93]. Since at present the worth and impact of its measurement remain poorly defined, three key points should be addressed to include this testing in clinical practice.

To whom: We now have enough information to endorse the importance of measuring the degree of LH for enhancing decision making in patient treatment. Hyperinflation significantly contributes to dyspnoea and exercise limitation. Furthermore, in severe cases, LH can seriously stress cardiopulmonary reserve, mainly on effort or under increased ventilatory demand such as in exacerbations [163]. However, as in other aspects of COPD, LH is not uniform in all patients, so that detection of the presence of LH can help to better define the clinical characterisation (non-hyperinflator and hyperinflator), thereby helping to obtain treatment more adapted to patient characteristics [164]. In clinical practice, some patients might benefit from personalized treatment with bronchodilators or supplemental oxygen, which reduces ventilatory demand and decreases the degree of dLH at any external workload. For this, measurement of LH should be recommended in all patients with dyspnoea in their daily life activities and in patients with frequent exacerbations, regardless of the values of FEV_1.

How: LH must be determined by measurement of lung volumes and it can be suspected by a reduction of IC. In 2005 a joint committee of the ATS/ERS published comprehensive guidelines for measuring lung volumes [165]. Although no single methodology was specifically recommended, in clinical practice body plethysmography is the reference method. It is more accurate than gas dilution methods in the presence of obstruction. Recently, a remarkable interest has been addressed to the IC since it is the only method available to evaluate exercise induced dLH. Moreover, it has been described that it can predict increased and overall mortality when the IC/TLC index falls to less than 25% [166]. Therefore IC is useful not only to assess changes in gas trapping for various therapies but is a prognostic factor for survival. Despite its simplicity it should be borne in mind that IC is an imperfect surrogate of body plethysmography for evaluating the reversibility of LH with bronchodilators [100].

When: in general, LH increases as airway obstruction worsens. However, there is not a linear relationship between them. At any stage of the disease, an improvement in LH can be observed after bronchodilators (measured by FRC or estimated by IC), which exceed that of the FEV_1, particularly in flow-limited patients [118]. These changes are related to improvement in symptoms and exercise limitation [49]. For this reason LH should be measured at any degree of the disease if the result can assist in making therapeutic decisions because it provides more useful information pertaining to dyspnoea and exercise tolerance than FEV_1, particularly when there are discrepancies between clinical features and impairment in airflow obstruction.

Special attention should be devoted to ventilator-dependent COPD patients in the critical care settings. In these conditions, assessment of dLH, and PEEPi, is crucial for appropriate setting of the ventilator pattern, prevention of patient-ventilator dissynchrony and successful weaning [167].

Conflict of interest

Andrea Rossi has received personal compensations for lectures and support for travelling to congresses from

Boehringer Ingelheim, Novartis, GlaxoSmithKlein, AstraZeneca, Chiesi Italia, Nycomed/Takeda, and support for research from GlaxoSmithKline, Novartis Italia, Chiesi Italia.

Marc Miravitlles has received speaker fees from Almirall, Boehringer Ingelheim, Pfizer, AstraZeneca, Chiesi, Esteve, GlaxoSmithKline, Menarini, Novartis, Talecris-Grifols, Takeda-Nycomed, and Novartis, and consulting fees from Almirall, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Gebro Pharma, MediImmune, Novartis, Talecris-Grifols and Takeda-Nycomed.

Zaurbek Aisanov has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Novartis, Sanofi, Takeda-Nycomed, Teva, Zambon, and consulting fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Takeda-Nycomed, Teva.

Nicolas Roche has received over the past 5 years fees for speaking, organising education, participation in advisory boards or consulting from Almirall, Nycomed-Takeda, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MEDA, MSD-Chibret, Mundipharma, Novartis, Pfizer, Teva; research grants from Novartis, Nycomed, Boehringer Ingelheim and Pfizer.

Sergey Avdeev has received speaker fees from Boehringer Ingelheim, AstraZeneca, Takeda-Nycomed, GlaxoSmithKline, Novartis, Chiesi, Pfizer, Bayer, Zambon, and consulting fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, and Takeda-Nycomed.

Giuseppe Di Maria has received personal consulting fees from Boerhinger Ingelheim Italy and GlaxoSmithKline. and has been granted for institutional research from Boerhinger Ingelheim in the past three years.

Thomas Similowski reports personal fees from AstraZeneca France/and Corporate, personal fees and non-financial support from Boerhinger Ingelheim France, grants, personal fees, non-financial support from Novartis France, personal fees from GlaxoSmithKline France and Chiesi France, non-financial support from Almirall France, grants, personal fees from Pierre Fabre, Medimmune, Menarini, and Pfizer France, all outside the submitted work.

Claudio F. Donner has received speaker fees and support for participating to Congresses from Almirall, Boehringer Ingelheim, GlaxoSmithKline, Novartis and TEVA and consulting fees from Boehringer Ingelheim, GlaxoSmithKline, Novartis and Pfizer.

Jose Luis Izquierdo has received speaker fees from Almirall, AstraZeeneca, Bayer, Boehringer Ingelheim, Chiesi, Esteve, GlaxoSmithKline, Menarini, Pfizer, Talecris-Grifols and Takeda-Nycomed, and consulting fees from Almirall, AstraZeeneca, Boehringer Ingelheim, GlaxoSmithKline, Pfizer, and Takeda-Nycomed.

Henrik Watz is an employee of the Pulmonary Research Institute. His institution received reimbursement from compensation received for participation in clinical studies from Almirall, AstraZeneca, AB2BIO, Bayer, Boehringer, GlaxoSmithkline, Intermune, Merck, Novartis, Revotar, Roche, Takeda. Henrik Watz received speaking honoraries, honoraries for participation in advisory board meetings, travel support for attending congresses in respiratory medicine, and unrestricted research grants from Almirall, BerlinChemie, Boehringer, Chiesi, AstraZeneca, GlaxoSmithkline, Merck, Novartis, Takeda.

Heinrich Worth received speaking honoraries, honoraries for participation in advisory board meetings, travel support for attending congresses in respiratory medicine, and unrestricted research grants from Almirall, BerlinChemie, Boehringer, Bionorica, AstraZeneca, Novartis, Takeda.

Acknowledgements

This publication has been supported by an unrestricted educational grant from Novartis. The sponsor had no role in the selection of authors, topics, discussions and writing of the manuscript. The manuscript has been written by the authors without any external support.

References

[1] Buist A, McBurnie M, Vollmer W, Gillespie S, Burney P, Mannino D, et al. International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. Lancet 2007;370:741—50.
[2] Murray CJL, Lopez AD. Measuring the global burden of disease. N Eng J Med 2013;369:448—57.
[3] Gagnon P, Guenette JA, Langer D, Laviolette L, Mainguy V, Maltais V, et al. Pathogenesis of hyperinflation in chronic obstructive pulmonary disease. Int J Chron Obs Pulm Dis 2014;9:187—201.
[4] Cooper BC. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med 2006;10A: S21—31.
[5] Watz H, Waschki B, Boehme C, Claussen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. Am J Respir Crit Care Med 2008;177:743—51.
[6] Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD — role of hyperinflation. Chest 2010;138:32—8.
[7] Static Agostoni E, Campbell EJM, Agostoni E, Newsom Davis J. The respiratory muscles. London: Lloyd-Luke; 1970. p. 138.
[8] Similowski T, Derenne JP, Milic-Emili J. Respiratory mechanics during acute respiratory failure of chronic obstructive pulmonary disease. In: Derenne JP, Whitelaw W, Similowski T, editors. Acute respiratory failure in chronic obstructive pulmonary disease. NY: Marcel Dekker; 1996. p. 23—46.
[9] Gibson GJ. Pulmonary hyperinflation a clinical overview. Eur Respir J 1996;9:2640—9.
[10] Celli BR. Pathophysiology of chronic obstructive pulmonary disease. In: Aliverti A, Brusasco V, Macklem PT, Pedotti A, editors. Mechanics of breathing pathophysiology, diagnosis, and treatment. Italia Milano: Springer-Verlag; 2002. p. 218—31.
[11] Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. Eur Respir J 1995;8:492—506.
[12] O'Donnell DE, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. Eur Respir Rev 2006;15:61—7.
[13] Carbonara P, Eidelman DH. Pulmonary statics in diseases. In: Hamid Q, Shannon J, Martin J, editors. Physiologic basis of respiratory diseases. Hamilton, Ont., Canada: Dekker Inc.; 2005. p. 69—76.
[14] De Troyer A, Pride NB. The chest wall and the respiratory muscles in COPD. In: Roussos Ch, editor. The thorax, part C:

disease. New York, NY, USA: Marcel Dekker Inc; 1995. p. 1975—2006.
[15] Macklem PT. Therapeutic implications of the pathophysiology of COPD. Eur Respir J 2010;35:676—80.
[16] Milic-Emili J, Torchio R, D'Angelo E. Closing volume: a reappraisal. Eur J Appl Physiol 2007;99:567—83.
[17] Calverley PMA, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. Eur Respir J 2005;25:186—99.
[18] Rossi A, Polese G, Brandi G, Conti G. Intrinsic positive end-expiratory pressure (PEEPi). Intensive Care Med 1995;21: 547—53.
[19] Khirani S, Polese G, Aliverti A, et al. On line monitoring of lung mechanics during spontaneous breathing: a physiologic study. Respir Med 2010;104:463—71.
[20] Marini JJ. Dynamic hyperinflation and auto-positive end-expiratory pressure. Lesson learned over 30 years. Am J Respir Crit Care Med 2011;184:756—62.
[21] Mughal MM, Culver DA, Minai OA, Arrolinga AC. Auto-positive end-expiratory pressure: mechanisms and treatment. Clevel Clin J Med 2005;72:801—9.
[22] Pride NB, Macklem PT. Lung mechanics in disease. In: Handbook of physiology, section 3 the respiratory system. The mechanics of breathing, part 2, vol. 3. Bethesda, Ma: American Physiological Society; 1986. p. 659—92.
[23] Anthonisen NR. Tests of mechanical function. In: Handbook of physiology, section 3 the respiratory system. The mechanics of breathing, part 2, vol. 3. Bethesda, Ma: American Physiological Society; 1986. p. 753—83.
[24] Appendini L, Purro A, Patessio A, et al. Partitioning of inspiratory muscle workload and pressure assistance in ventilator-dependent COPD patients. Am J Respir Crit Care Med 1996;154:1301—9.
[25] Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? Eur Respir J 2012;40:322—9.
[26] Laveneziana P, Webb KA, Wadell K, Neder JA, O'Donnell DE. Does expiratory muscle activity influence dynamic hyperinflation and exertional dyspnea in COPD? Respir Physiol Neurobiol 2014;199:24—33.
[27] De Troyer A. Effect of hyperinflation on the diaphragm. Eur Respir J 1997;10:708—13.
[28] Dal Vecchio L, Polese G, Poggi R, Rossi A. Intrinsic positive end-expiratory pressure in stable patients with chronic obstructive pulmonary disease. Eur Respir J 1990; 3:74—80.
[29] Haluszka J, Chartrand D, Grassini A, Milic-Emili J. Intrinsic PEEP and arterial PCO2 in stable patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1990;141: 1194—7.
[30] Wedzicha JA, Decramer M, Seemugal TA. The role of bronchodilator treatment in the prevention of exacerbations of COPD. Eur Respir J 2012;40:1545—54.
[31] ATS, ERS, ESICM, SRLF. International consensus conference in intensive care medicine: noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 2001;163:283—91.
[32] Levine S, Kaiser L, Leferovich J, Tikunov B. Cellular adaptation in the diaphragm in chronic obstructive pulmonary disease. N Eng J Med 1997;337:1799—806.
[33] Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. N Eng J Med 1991;325:917—23.
[34] Kawagoe Y, Permutt S, Fessler HE. Hyperinflation with intrinsic PEEP and respiratory muscle blood flow. J Appl Physiol 1994;77:2440—8.
[35] Brandolese R, Broseghini C, Polese G, Bernasconi M, Brandi G, Milic-Emili J, Rossi A. Effects of intrinsic PEEP on pulmonary gas exchange in mechanically-ventilated patients. Eur Respir J 1993;6:358—63.
[36] Rodriguez-Roisin R, MacNee W. Pathophysiology of chronic obstructive pulmonary disease. Eur Respir Mon 2006;11: 177—200.
[37] Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, et al. Ventilation—perfusion mismatching and COPD staging severity. J Appl Physiol 2009;106:1902—8.
[38] Ranieri MV, Dambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. Eur Respir J 1996;9:1283—92.
[39] Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE. An official American thoracic society statement: update on the mechanisms, assessment, and management of dyspnoea. Am J Respir Crit Care Med 2012;185:435—52.
[40] Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnoea: review and hypotheses. Respir Physiol Neurobiol 2009;167:53—60.
[41] Burgel PR, Escamilla R, Perez T, Carre P, Caillaud D, Chanez P, Pinet C, Jebrak G, Brinchault G, Court-Fortune I, Paillasseur JL, Roche N. Impact of comorbidities on COPD-specific health-related quality of life. Respir Med 2013;107: 233—41.
[42] Dijk WD, Bemt L, Haak-Rongen S, Bischoff E, Weel C, Veen JC, Schermer TR. Multidimensional prognostic indices for use in COPD patient care. A systematic review. Respir Res 2011;12:151.
[43] Sundh J, Janson C, Lisspers K, Stallberg B, Montgomery S. The dyspnoea, obstruction, smoking, exacerbation (DOSE) index is predictive of mortality in COPD. Prim Care Respir J 2012;21:295—301.
[44] Roche N, Zureik M, Soussan D, Neukirch F, Perrotin D. Predictors of outcomes in COPD exacerbation cases presenting to the emergency department. Eur Respir J 2008; 32:953—61.
[45] Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnoea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121:1434—40.
[46] Laveneziana P, Bruni GI, Presi I, Stendardi L, Duranti R, Scano G. Tidal volume inflection and its sensory consequences during exercise in patients with stable asthma. Respir Physiol Neurobiol 2013;185:374—9.
[47] Laveneziana P, Webb KA, Ora J, Wadell K, O'Donnell DE. Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. Am J Respir Crit Care Med 2011;184:1367—73.
[48] Banzett RB, Pedersen SH, Schwartzstein RM, Lansing RW. The affective dimension of laboratory dyspnea: air hunger is more unpleasant than work/effort. Am J Respir Crit Care Med 2008;177:1384—90.
[49] Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the medical research council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54: 581—6.
[50] Calverley PMA. Dynamic hyperinflation: is it worth measuring? Proc Am Thorac Soc 2006;3(3):239—44.
[51] Jensen D, Alsuhail A, Viola R, Dudgeon DJ, Webb KA, O'Donnell DE. Inhaled fentanyl citrate improves exercise endurance during high-intensity constant work rate cycle exercise in chronic obstructive pulmonary disease. J Pain Symptom Manage 2012;43(4):706—19.
[52] Carrieri-Kohlman V, Gormley JM, Eiser S, Demir-Deviren S, Nguyen H, Paul SM, Stulbarg MS. Dyspnoea and the affective response during exercise training in obstructive pulmonary disease. Nurs Res 2001;50(3):136—46.

[53] O'Donnell DE. Ventilatory limitations in chronic obstructive pulmonary disease. Med Sci Sports Exerc 2001;33:S647—55.
[54] Marin JM, Carrizo SJ, Gascon M, Sanchez A, Gallego B, Celli BR. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163:1395—9.
[55] Hannink JD, van Helvoort HA, Dekhuijzen PN, Heijdra YF. Dynamic hyperinflation during daily activities: does COPD global initiative for chronic obstructive lung disease stage matter? Chest 2010;137:1116.
[56] Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnoea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:622—9.
[57] Guenette JA, Chin RC, Cheng S, et al. Mechanism of exercise intolerance in global initiative for chronic obstructive lung disease grade 1 COPD. Eur Respir J 2014;44:1177—87.
[58] Younes M, Kivinen G. Respiratory mechanics and breathing pattern during and following maximal exercise. J Appl Physiol Respir Environ Exerc Physiol 1984;57:1773.
[59] Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulm Med 2013. http://dx.doi.org/10.1155/2013/956081. Article ID 956081.
[60] O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:770—7.
[61] Johnson BD, Beck KC, Zeballos RJ, Weisman IM. Advances in pulmonary laboratory testing. Chest 1999;116:1377—87.
[62] O'Donnell DE. Assessment of bronchodilator efficacy in symptomatic COPD. Chest 2000;117:42S—7S.
[63] Ora J, Laveneziana P, Ofir D, Deesomchok A, Webb KA, O'Donnell DE. Combined effects of obesity and chronic obstructive pulmonary disease on dyspnea and exercise tolerance. Am J Respir Crit Care Med 2009;180:964—71.
[64] Seemugal TAR, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161:1608—13.
[65] Parker CM, Voduc N, Aaron SD, Webb KA, O'Donnell DE. Physiologic changes during symptom recovery from moderate exacerbations of COPD. Eur Respir J 2005;26:420—8.
[66] Stevenson NJ, Walker PP, Costello RW, Calverley PMA. Lung mechanics and dyspnoea during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172:1510—6.
[67] Rossi A, Polese G, Milic-Emili J. Monitoring respiratory mechanics in ventilator dependent patients. In: Tobin MJ, editor. Principles and practice of intensive care monitoring. New York, NY: McGraw Hill; 1998. p. 553—96.
[68] Kimball WR, Leith DE, Robins AD. Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. Am Rev Respir Dis 1982;126:991—5.
[69] Tuxen DV, Lane S. The effect of ventilatory pattern on hyperinflation, airway pressure, and circulation in mechanical ventilation in patients with severe airflow obstruction. Am Rev Respir Dis 1987;136:872—9.
[70] Broseghini C, Brandolese R, Poggi R, Polese G, Manzin E, Milic-Emili J, Rossi A. Respiratory mechanics during the first day of mechanical ventilation in patients with pulmonary edema and chronic airway obstruction. Am Rev Respir Dis 1988;138:355—61.
[71] Gottfried SB, Rossi A, Higgs BD, Calverley PMA, Zocchi L, Bozic C, Milic-Emili J. Non invasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 1985;131:414—20.
[72] Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. Am Rev Respir Dis 1982;126:166—70.
[73] Purro A, Appendini L, De Gaetano A, Gudjonsdottir M, Donner CF, Rossi A. Physiologic determinants of ventilator dependence in long-term mechanically ventilated patients. Am J Respir Crit Care Med 2000;161:1115—23.
[74] Albert RK, Muramoto A, Caldwell J, Koepsell T, Butler J. Increases in intrathoracic pressure do not explain the rise in left ventricular end-diastolic pressure that occurs during exercise in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1985;132:623—7.
[75] Butler J, Schrijen F, Henriquez A, Polu JM, Albert RK. Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. Am Rev Respir Dis 1988;138:350—4.
[76] Butler J, Schrijen F, Henriquez A, Polu JM, Albert RK. Cause of increased right and left atrial pressures in patients with obstructed airflow disease. Chest 1988;93:171S—2S.
[77] Criner GJ, Scharf SM, Falk JA, Gaughan JP, Sternberg AL, Patel NB, Fessler HE, Minai OA, Fishman AP. Effect of lung volume reduction surgery on resting pulmonary hemodynamics in severe emphysema. Am J Respir Crit Care Med 2007;176:253—60.
[78] Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M, Sainty JM, Orehek J. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. Am J Respir Crit Care Med 2000;162:670—5.
[79] Funk GC, Lang I, Schenk P, Valipour A, Hartl S, Burghuber OC. Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. Chest 2008;133:1354—9.
[80] Lopez-Sanchez M, Munoz-Esquerre M, Huertas D, Gonzalez-Costello J, Ribas J, Manresa F, Dorca J, Santos S. High prevalence of left ventricle diastolic dysfunction in severe COPD associated with a low exercise capacity: a cross-sectional study. PLoS ONE 2013;8:e68034.
[81] Jorgensen K, Houltz E, Westfelt U, Nilsson F, Schersten H, Ricksten SE. Effects of lung volume reduction surgery on left ventricular diastolic filling and dimensions in patients with severe emphysema. Chest 2003;124:1863—70.
[82] Jorgensen K, Muller MF, Nel J, Upton RN, Houltz E, Ricksten SE. Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study. Chest 2007;131:1050—7.
[83] Jorgensen K, Houltz E, Westfelt U, Ricksten SE. Left ventricular performance and dimensions in patients with severe emphysema. Anesth Analg 2007;104:887—92.
[84] Thurlbeck WM, Simon G. Radiographic appearance of the chest in emphysema. Am J Roentgenol 1978;130:429—40.
[85] Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, Jiang R, Kawut SM, Kronmal RA, Lima JA, Shahar E, Smith LJ, Watson KE. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med 2010;362:217—27.
[86] Grau M, Barr RG, Lima JA, Hoffman EA, Bluemke DA, Carr JJ, Chahal H, Enright PL, Jain A, Prince MR, Kawut SM. Percent emphysema and right ventricular structure and function: the multi-ethnic study of atherosclerosis-lung and multi-ethnic study of atherosclerosis-right ventricle studies. Chest 2013;144:136—44.
[87] Smith BM, Prince MR, Hoffman EA, Bluemke DA, Liu CY, Rabinowitz D, Hueper K, Parikh MA, Gomes AS, Michos ED, Lima JA, Barr RG. Impaired left ventricular filling in COPD and Emphysema: Is it the heart or the lungs?: The multi-ethnic study of atherosclerosis COPD study. Chest 2013;144:1143—51.

[88] Vassaux C, Torre-Bouscoulet L, Zeineldine S, Cortopassi F, Paz-Diaz H, Celli BR, Pinto-Plata VM. Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD. Eur Respir J 2008;32:1275—82.
[89] Travers J, Laveneziana P, Webb KA, Kesten S, O'Donnell DE. Effect of tiotropium bromide on the cardiovascular response to exercise in COPD. Respir Med 2007;101:2017—24.
[90] Lammi MR, Ciccolella D, Marchetti N, Kohler M, Criner GJ. Increased oxygen pulse after lung volume reduction surgery is associated with reduced dynamic hyperinflation. Eur Respir J 2012;40:837—43.
[91] Gea J, Agusti A, Roca J. Pathophysiology of muscle dysfunction in COPD. J Appl Physiol 2013;114:1222—34.
[92] Donaldson AV, Maddocks M, Martolini D, Polkey MI, Man WD. Muscle function in COPD: a complex interplay. Int J Chron Obs Pulm Dis 2012;7:523—35.
[93] Garcia-Rio F, Lores V, Mediano O, Rojo B, Hernanz A, Lopez-Collazo E, Alvarez-Sala R. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. Am J Respir Crit Care Med 2009;180:506—12.
[94] Garcia-Pachon E. Paradoxical movement of the lateral rib margin (Hoover sign) for detecting obstructive airway disease. Chest 2002;122:651—5.
[95] Maury G, Marchand E. Distension thoracique et BPCO, au-delà de la mécanique respiratoire et de la dyspnée. Rev Mal Respir 2009;26:153—5.
[96] Thoman RL, Stoker GL, Ross JC. The efficacy of pursed-lips breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1966;93:100—6.
[97] Campbell EJM. Physical signs of diffuse airways obstruction and lung distension. Thorax 1969;24:1—3.
[98] Rodenstein DO, Stanescu DC, Francis C. Demonstration of failure of body plethysmography in airway obstruction. J Appl Physiol 1982;52:949—54.
[99] Brown R, Leith DE, Enright PL. Multiple breath helium dilution measurement of lung volumes in adults. Eur Respir J 1998;11:246—55.
[100] Perez T, Guenard H. Comment mesurer et suivre la distensión pulmonaire aucours de la BPCO. Rev Mal Respir 2009;26:381—93.
[101] O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:542—9.
[102] O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 2004;23:832—40.
[103] Clausen J. Measurement of absolute lung volumes by imaging techniques. Eur Respir J 1997;10:2427—31.
[104] Webb WR. Radiology of obstructive pulmonary disease. Am J Radiol 1997;169:637—47.
[105] Garfield JL, Marchetti N, Gaughan JP, Steiner RM, Criner GJ. Total lung capacity by plethysmography and high-resolution computed tomography in COPD. Int J COPD 2012;7:119—26.
[106] O'Donnell CR, Bankier AA, Stiebellehner L, Reilly JJ, Brown R, Loring SH. Comparison of plethysmographic and helium dilution lung volumes: which is best for COPD? Chest 2010;137:1108—15.
[107] Siddiqui S, Usmani OS. Small airways, big challenge: measuring the unseen? Nat Med 2012;18:1619—21.
[108] Galbàn CJ, Han MK, Boes JL, et al. Computer tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. Nat Med 2012;18:1711—5.
[109] Nucci G, Mergoni M, Bricchi C, Polese G, Corbelli C, Rossi A. Online monitoring of intrinsic PEEP in ventilator-dependent patients. J Appl Physiol 2000;89:985—95.
[110] Brochard L. Intrinsic (or auto-) positive end-expiratory pressure during spontaneous or assisted ventilation. Intensive Care Med 2002;28:1552—4.
[111] Tobin M, Brochard L, Rossi A. Assessment of respiratory muscle function in the intensive care unit. Am J Respir Crit Care Med 2002;166:610—24. ATS/ERS statement on respiratory muscle testing.
[112] Appendini L, Confalonieri M, Rossi A. Clinical relevance of monitoring respiratory mechanics in the ventilator-supported patient: an update (1995—2000). Curr Opin Crit Care 2001;7:41—8.
[113] Akoumianaki E, Maggiore SM, Valenza F, et al. The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med 2014;189:520—31.
[114] Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Viellard-Baron A, Welte T. Weaning from mechanical ventilation. Eur Respir J 2007;29:1033—56.
[115] Ramsdell JW, Tisi GM. Determination of bronchodilation in the clinical pulmonary function laboratory. Role of changes in static lung volumes. Chest 1979;76:622—8.
[116] Lougheed MD, Lam M, Forkert L, Webb KA, O'Donnell DE. Breathlessness during acute bronchoconstriction in asthma. Pathophysiologic mechanisms. Am Rev Respir Dis 1993;148:1452—9.
[117] Hatipoglu U, Laghi F, Tobin MJ. Does inhaled albuterol improve diaphragmatic contractility in patients with chronic obstructive pulmonary disease? Am J Respir Crit Care Med 1999;160:1916—21.
[118] Brusasco V, Pellegrino R, Rodarte JR. Vital capacities in acute and chronic airway obstruction: dependence on flow and volume histories. Eur Respir J 1997;10:1316—20.
[119] O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;158:1557—65.
[120] Thomas M, Decramer M, O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD. Prim Care Respir J 2013;22:101—11.
[121] Bateman E, Ferguson G, Barnes N, Gallagher N, Green Y, Henley M, Banerji D. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 2013;42:1484—94.
[122] Bateman ED, Kornmann O, Ambery C, Norris V. Pharmacodynamics of GSK961081, a bi-functional molecule, in patients with COPD. Pulm Pharmacol Ther 2013;26:581—7.
[123] Beeh K-M, Korn S, Beier J, Jadayel D, Henley M, D'Andrea P, Banerji D. Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: the BRIGHT study. Respir Med 2014;108:584—92.
[124] Jones PW, Beeh KM, Chapman KR, Decramer M, Mahaler D, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med 2014;189:250—5.
[125] O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, Knobil K. Effect of fluticasone propionate/-salmeterol on lung hyperinflation and exercise endurance in COPD. Chest 2006;130:647—56.
[126] Worth H, Förster K, Eriksson G, Nihlén U, Peterson S, Magnussen H. Budesonide added to formoterol contributes to improved exercise tolerance in patients with COPD. Respir Med 2010;104:1450—9.
[127] John M, Bosse S, Oltmanns U, Schumacher A, Witt C. Effects of inhaled HFA beclomethasone on pulmonary function and symptoms in patients with chronic obstructive pulmonary disease. Respir Med 2005;99:1418—24.
[128] Tzani P, Crisafulli E, Nicolini G, Aiello M, Chetta A, Clini EM, Olivieri D. Effects of beclomethasone/formoterol fixed

combination on lung hyperinflation and dyspnoea in COPD patients. Int J Chron Obs Pulm Dis 2011;6:503—9.
[129] O'Donnell DE, Bredenbröker D, Brose M, Webb KA. Physiological effects of roflumilast at rest and during exercise in COPD. Eur Respir J 2012;39:1104—12.
[130] Fink G, Kaye C, Sulkes J, Gabbay U, Spitzer SA. Effect of theophylline on exercise performance in patients with severe chronic obstructive pulmonary disease. Thorax 1994;49:332—4.
[131] Murciano D, Auclair MH, Pariente R, Aubier M. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. N Engl J Med 1989;320:1521—5.
[132] Voduc N, Alvarez GG, Amjadi K, Tessier C, Sabri E, Aaron SD. Effect of theophylline on exercise capacity in COPD patients treated with combination long-acting bronchodilator therapy: a pilot study. Int J Chron Obs Pulm Dis 2012;7:245—52.
[133] Santus P, Centanni S, Verga M, di Marco F, Matera MG, Cazzola M. Comparison of the acute effect of tiotropium versus a combination therapy with single inhaler budesonide/formoterol on the degree of resting pulmonary hyperinflation. Respir Med 2006;100:1277—81.
[134] Bianchi L, Foglio K, Pagani M, Vitacca M, Rossi A, Ambrosino N. Effects of proportional assist ventilation on exercise tolerance in COPD patients withchronic hypercapnia. Eur Respir J 1998;11:422—7.
[135] Casaburi R, Gosselink R. skeletal muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:S1—40.
[136] Garrod R, Dallimore K, Cook J, Davies V, Quade K. An evaluation of the acute impact of pursed lips breathing on walking distance in nonspontaneous pursed lips breathing chronic obstructive pulmonary disease patients. Chron Respir Dis 2005;2:67—72.
[137] Stevenson NJ, Calverley PM. Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease. Thorax 2004;59:668—72.
[138] Spruit MA, Singh SJ, Garvey C, Zuwallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Mölken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF, ATS/ERS Task Force on Pulmonary Rehabilitation. An official American thoracic society/European respiratory society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188:13—64.
[139] Casaburi R, ZuWallack R. Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. N Engl J Med 2009;360:1329—35.
[140] Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 2005;128:2025—34.
[141] Gigliotti F, Coli C, Bianchi R, Romagnoli I, Lanini B, Binazzi B, Scano G. Exercise training improves exertional dyspnoea in patients with COPD: evidence of the role of mechanical factors. Chest 2003;123:1794—802.
[142] Puente-Maestu L, Sánz ML, Sánz P, Ruíz de Oña JM, Rodríguez-Hermosa JL, Whipp BJ. Comparison of effects of supervised versus self-monitored training programs in patients with chronic obstructive pulmonary disease. Eur Respir J 2000;15:517—25.
[143] Ruiz de Oña Lacasta JM, Garcia de Pedro J, Puente-Maestu L, Llorente Iñigo D, Celdrán Gil J, Cubillo Marcos JM. Effects of muscle training on breathing pattern in patients with severe chronic obstructive pulmonary disease. Arch Bronconeumol 2004;40:20—3.
[144] Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. Eur Respir J 2002;20:12—9.
[145] Dean NC, Brown JK, Himelman RB, Doherty JJ, Gold WM, Stulbarg MS. Oxygen may improve dyspnoea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. Am Rev Respir Dis 1992;146:941—5.
[146] O'Donnell DE, Bertley JC, Chau LK, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. Am J Respir Crit Care Med 1997;155:109—15.
[147] Palange P, Valli G, Onorati P,Antonucci R, Paoletti P, Rosato A, Manfredi F, Serra P. Effect of helix on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. J Appl Physiol 2004;97:1637—42.
[148] Cooper JD, Patterson GS, Sundaresan RS, Trulock EP, Yusen RD, Kaczka DW, Ingenito EP, Lutchen KR, Pohl MS, Lefrak SS. Results of 150 consecutive bilateral lung volume tory impedance during mechanical ventilation: implications for flow reduction procedures in patients with severe emphysema. J Thorac Cardiovasc Surg 1996;112:1319—29.
[149] Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE, National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059—73.
[150] Hopkinson NS, Toma TP, Hansell DH, Goldstraw P, Moxham J, Geddes DM, Polkey MI. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Respir Crit Care Med 2005;171:453—60.
[151] Petrof BJ, Calderini E, Gottfried SB. Effect of CPAP on respiratory effort and dyspnea during exercise in severe COPD. J Appl Physiol 1985;1990(69):179—88.
[152] van't Hul AJ, Kwakkel G, Gosselink R. The acute effects of non-invasive ventilatory support during exercise on exercise endurance and dyspnoea in patients with COPD: a systematic review. J Cardiopulm Rehabil 2002;22:290—7.
[153] Coussa ML, Guerin C, Eissa NT, et al. Partitioning of work of breathing in mechanically ventilated COPD patients. J Appl Physiol 1993;75:1711—9.
[154] Jolliet P, Tassaux D, Thouret JM, Chevrolet JC. Beneficial effects of helium: oxygen versus air: oxygen noninvasive pressure support in patients with descompensated chronic obstructive pulmonary disease. Crit Care Med 1999;27:2422—9.
[155] Kyroussis D, Polkey MI, Hamnegard CH, Mills GH, Green M, Moxham J. Respiratory muscle activity in patients with COPD walking to exhaustion with and without pressure support. Eur Respir J 2000;15:649—55.
[156] Maltais F, Reissmann H, Gottfried SB. Pressure support reduces inspiratory effort and dyspnoea during exercise in chronic airflow obstruction. Am J Respir Crit Care Med 1995;151:1027—33.
[157] van't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Acute effects of inspiratory pressure support during exercise in patients with COPD. Eur Respir J 2004;23:34—40.
[158] Puente-Maestu L, Martínez Y, Pedraza F, Sánchez G, Stringer WW. A controlled trial of the effects of leg training on breathing pattern and dynamic hyperinflation in severe COPD. Lung 2006;184:159—67.
[159] Dolmage TE, Goldstein RS. Repeatability of inspiratory capacity during incremental exercise in patients with severe COPD. Chest 2002;121:708—14.

[160] Appendini L, Patessio A, Zanaboni S, Carone M, Gukov B, Donner CF, Rossi A. Physiologic effects of positive end-expiratory pressure and mask pressure during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149:1069—76.
[161] Appendini L, Purro A, Gudjonsdottir M, Baderna P, Patessio A, Zanaboni S, Donner CF, Rossi A. Physiologic response of ventilator-dependent patients with chronic obstructive pulmonary disease to proportional assist ventilation and continuous positive airway pressure. Am J Respir Crit Care Med 1999;159:1510—7.
[162] Diaz O, Begin P, Torrealba B, Jover E, Lisboa C. Effects of noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. Eur Respir J 2002;20:1490—8.
[163] O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. COPD 2006;3:219—32.
[164] Ruppel GL. What is the clinical value of lung volumes? Respir Care 2012;57:26—38.
[165] Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511—22.
[166] Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predict mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;171:591—7.
[167] Khirani S, Georgopoulos D, Rossi A, Moxham J. Ventilatory support in chronic obstructive pulmonary disease: invasive and noninvasiveSiafakas NM, editor. Management of chronic obstructive pulmonary disease. Eur Respir Mon 2006;11/38:401—29.