Why Does the Lung Hyperinflate?

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Patients with chronic obstructive pulmonary disease (COPD) often have some degree of hyperinflation of the lungs. Hyperinflated lungs can produce significant detrimental effects on breathing, as highlighted by improvements in patient symptoms after lung volume reduction surgery. Measures of lung volumes correlate better with impairment of patient functional capabilities than do measures of airflow. Understanding the mechanisms by which hyperinflation occurs in COPD provides better insight into how treatments can improve patients' health. Both static and dynamic processes can contribute to lung hyperinflation in COPD. Static hyperinflation is caused by a decrease in elasticity of the lung due to emphysema. The lungs exert less recoil pressure to counter the recoil pressure of the chest wall, resulting in an equilibrium of recoil forces at a higher resting volume than normal. Dynamic hyperinflation is more common and can occur independent of or in addition to static hyperinflation. It results from air being trapped within the lungs after each breath due to a disequilibrium between the volumes inhaled and exhaled. The ability to fully exhale depends on the degree of airflow limitation and the time available for exhalation. These can both vary, causing greater hyperinflation during exacerbations or increased respiratory demand, such as during exercise. Reversibility of dynamic hyperinflation offers the possibility for intervention. Use of bronchodilators with prolonged durations of action, such as tiotropium, can sustain significant reductions in lung inflation similar in effect to lung volume reduction surgery. How efficacy of bronchodilators is assessed may, therefore, need to be reevaluated.

Keywords: chronic obstructive pulmonary disease; dyspnea; functional residual capacity; hyperinflation; respiratory mechanics; work of breathing

Chronic obstructive pulmonary disease (COPD) is characterized by reduced expiratory airflows as measured by a reduced ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC). Although measurements of airflows are essential for the diagnosis of COPD and commonly used in disease staging, the effects of the disease on lung volumes correlate better with patient symptoms and impairment of functional capabilities (1, 2). The lungs in patients with COPD can be hyperinflated, either at rest or during exercise, causing several detrimental effects, including impairment of respiratory muscle function and gas exchange, and increases in the work of breathing. The benefits of reducing hyperinflation in COPD are best demonstrated by improvements in symptoms of patients after lung volume reduction surgery (3, 4). Indeed, the study of lung volumes in patients with COPD can give us a better understanding of the disease and how treatments work to improve our patients' health, and can also offer additional insight into how to better treat our patients.

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LUNG VOLUMES

Lung volumes can be divided into several compartments defined by the normal cycle of tidal breathing and the maximum capacity to inhale and exhale (Figure 1). During relaxed tidal breathing, the lungs tend to return to a basal level of inflation, which is termed the functional residual capacity (FRC) or end-expiratory lung volume (EELV). In normal lungs, this volume represents the point at which all respiratory muscles are at rest and equilibrium is achieved between the outward recoil of the chest wall and the inward recoil of the lungs (Figure 2). This specific physiologic volume is also termed the relaxation volume (5).

Once the FRC or EELV has been measured and is known, all other lung volumes, as shown in Figure 1, can be determined from traditional spirometry measurements. These include the total lung capacity (TLC), which is the maximum volume of air capable of being inhaled, and the residual volume (RV), which is the volume of air remaining in the lung at the end of complete exhalation. Of particular importance is the inspiratory capacity (IC), which represents the range where the majority of active tidal volume (V_T) recruitment occurs and can be regarded as the volume available for inspiration after FRC is subtracted from TLC. Because changes in TLC within an individual are usually small over short periods of time, it is possible to make inferences about what is happening to FRC or EELV from measurements of IC alone. This is of particular importance when making assessments in many clinical situations, where direct measurement of FRC or EELV using body box or inert gas dilution is not available or is impractical. Unfortunately, IC is rarely measured alone or as a routine part of spirometry in patients with COPD, despite its functional importance (discussed below).

STATIC AND DYNAMIC HYPERINFLATION

Hyperinflation of the lung is defined in various ways, but is commonly considered to be an elevation above normal of the resting FRC or EELV. Most, if not all, patients with COPD have some degree of hyperinflation of the lung, which often remains undetected in the absence of detailed physiologic analysis. Both static and dynamic effects of breathing contribute to lung hyperinflation in COPD.

Static hyperinflation results from decreased elasticity of the lung parenchyma. The alveoli and airways of normal lungs are elastic and well tethered by connective tissue, which not only helps to keep airways open during exhalation, but also provides the lung recoil to counter chest wall recoil (Figure 2). In COPD, destruction of elastic tissue commonly associated with emphysematous changes in the lung alters lung recoil, shifting the relationship between lung volume and distending pressure (pressure–volume curve) so that a given lung volume produces a lesser recoil pressure than in the healthy lung. This shift in lung recoil and its pressure–volume curve alters the balance between the opposing recoil pressures of the chest wall and the lung (5). Hence, the reduced lung recoil pressure requires a greater volume to balance the chest wall recoil, increasing FRC (Figure 2). Nevertheless, emphysema-associated static hyperinflation is only a modest

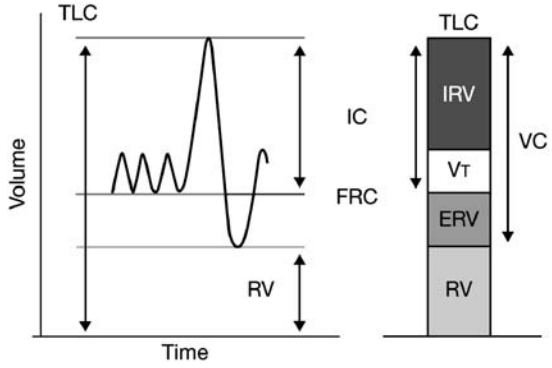

Figure 1. Lung volume measurements. The relationship between volumes obtained during a spirometric vital capacity (VC) maneuver and total lung capacity (TLC). Although spirometry measures VC and its components, it cannot measure absolute lung volumes, including residual volume (RV), functional residual capacity (FRC) or total lung capacity (TLC). Note that inspiratory capacity (IC) is inversely related to FRC, allowing an indirect inference on changes in FRC. ERV = expiratory reserve volume; IRV = inspiratory reserve volume; V_T = tidal volume.

contributor to hyperinflation in all but the most severe patients or patients with α_1-antitrypsin deficiency.

In contrast, dynamic hyperinflation, which occurs either independent of or in addition to static hyperinflation, can be observed as a key component of COPD pathophysiology in patients with all severities of COPD. Dynamic hyperinflation occurs when patients commence inhalation before full exhalation has been achieved. Consequently, air is trapped within the lungs with each successive breath. EELV no longer occurs at the passive point of equilibrium between chest wall and lung recoil, but occurs at a positive end-expiratory pressure (PEEP) before exhalation can achieve the relaxation volume (Figure 2). This concept is most commonly recognized in patients treated with positive-pressure ventilation in intensive care units (6). In these cases, failure to allow sufficient time for passive exhalation to the relaxation volume between inflations of the lungs causes intrinsic PEEP, progressive hyperinflation, and many associated detrimental effects. Such patients require regular monitoring to identify intrinsic PEEP and to prevent the escalation of dynamic hyperinflation.

Dynamic hyperinflation is dependent on expiratory airflows and expiratory time. In normal lungs, expiratory airflows are sufficient to allow for complete exhalation of the inhaled volume before the next inhalation is required, even when breathing at close to maximal ventilation. As minute ventilation increases to accommodate increased respiratory demands, V_T expands higher into the IC (Figure 3) (2). In healthy, younger subjects, forcible exhalation may also encroach into the expiratory reserve volume (ERV), resulting in a transient reduction of EELV and a negative end-expiratory pressure. Normally, however, EELV (and, therefore, IC) remains relatively static as minute ventilation increases. Thus, V_T is able to steadily expand to achieve greater minute ventilation whenever demanded.

In COPD, expiratory airflows are limited by airway narrowing resulting from increases in cholinergic (vagal) tone, inflammation, and mucus plugging. When combined with more collapsible airways (seen mainly in more severe patients), this increase in resistance to expiratory airflows prolongs the time required to exhale a given volume of air. In mild COPD, expiratory airflows may still be sufficient to allow complete exhalation of V_T to the relaxation volume when breathing frequency is low while at rest. However, whenever demand for a greater minute ventilation increases tidal volume and respiratory rate, the time available for exhalation can become insufficient, resulting in an increase in EELV and a reduced IC. Onset of dynamic hyperinflation will occur at ever lower minute ventilations as disease severity limiting exhalation worsens, even occurring during quiet breathing in severe patients. This is shown schematically on the right-hand side of Figure 3 in a patient with severe COPD and a degree of hyperinflation at rest (through a combination of both static and dynamic processes) (2). Resting hyperinflation is easily recognized by the increased EELV and reduced resting IC compared with the normal patient, despite an increase in TLC. Importantly, any desired recruitment of V_T becomes restricted with a limited opportunity to expand to greater volumes as EELV

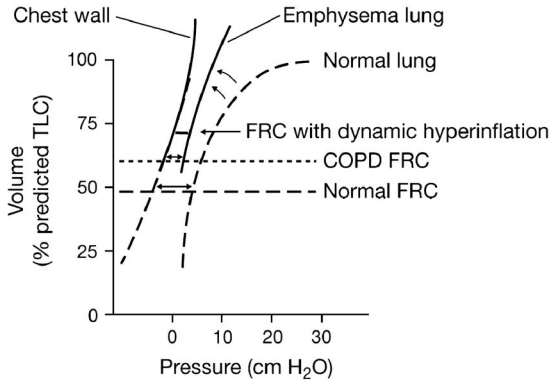

Figure 2. Effect of increased lung compliance on FRC. Normally, FRC in normal lungs occurs at the lung volume where equilibrium between recoil pressures of the chest wall and lungs is achieved with the respiratory muscles at rest (*long-dashed lines*). This is also called the resting volume. Loss of lung elasticity due to emphysema in COPD reduces the lung recoil pressure. Consequently, FRC or resting volume occurs at a higher volume, which defines static hyperinflation (*short-dashed lines*). Dynamic hyperinflation occurs when end expiratory lung volume (EELV) or FRC is unable to return to the resting volume, resulting in a positive end-expiratory pressure (PEEP). TLC = total lung capacity.

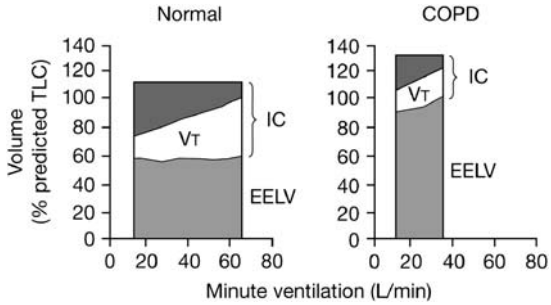

Figure 3. Dynamic changes in lung volumes during exercise in normal lungs and COPD. Note that end-expiratory lung volume (EELV) remains relatively constant in normal lungs as minute ventilation increases. Tidal volume (V_T) is able to expand, since inspiratory volume (IC) remains constant. In COPD, increases in EELV force V_T closer to the total lung capacity (TLC) and IC is reduced even at rest. Dynamic hyperinflation further increases EELV and reduces IC as minute ventilation increases. V_T is unable to expand and patients cannot achieve high minute ventilations before breathing becomes so restricted that patients have to stop activity. Adapted with permission from Reference 2.

nears TLC. In addition, airflow limitation prevents even transient recruitment from the ERV. With a limited IC, increases in minute ventilation can only be achieved through an increase in respiratory rate. However, as respiratory rate increases, expiratory time is further decreased and a vicious cycle of gas trapping and progressive dynamic hyperinflation occurs. The ability of patients with COPD to increase minute ventilation is, therefore, severely compromised.

By definition, the degree of dynamic hyperinflation at any moment in time varies depending on the degree of airflow limitation and the rate of breathing. Hence, patients may become more hyperinflated during exacerbations of COPD, or they may become less hyperinflated when the rate of breathing is reduced, such as during periods of rest between activity. Since dynamic hyperinflation can be reversible, it is an attractive goal for any therapeutic interventions.

HYPERINFLATION AND WORK OF BREATHING

In addition to a reduction in IC, lung hyperinflation also increases the work of breathing. This is illustrated in modified Campbell diagrams (7) showing the relationship between lung volume and (pleural) pressure during tidal breathing in normal and hyperinflated lungs (Figure 4). The area of the pressure–volume loops represents the work of breathing. The Campbell diagram plots the recoil pressures exerted by the chest wall (static chest wall compliance, Cw) and the lungs (dynamic lung compliance, $C_{L_{dyn}}$; plotted as the mirror image to the lung recoil pressure shown in Figure 2). In this example, $C_{L_{dyn}}$ is plotted as a straight line joining the points representing the beginning and end of inspiratory flow (zero flow), at which point the pressure is equal and opposite to the lung recoil pressure. This allows graphical visualization of the amount of work required to overcome the combined elastic recoil of the chest wall and lungs during inhalation as indicated by the shaded area between Cw and C_L. As suggested by the divergence of the two recoil pressures in Figures 2 and 4, the amount of elastic work increases as lung volume increases. In addition to elastic pressures, the shape of the pressure–volume loops, and therefore the work of breathing, can vary depending on how forcefully an inhalation (extending the curve to the left) or exhalation (extending the curve to the right) effort is performed.

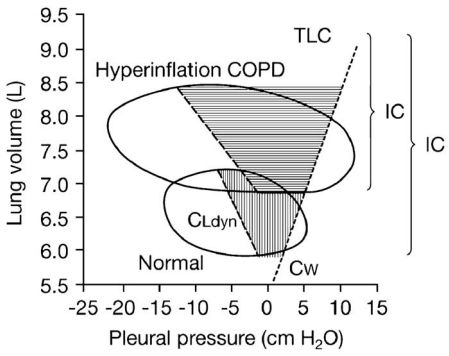

Figure 4. Effect of hyperinflation on work of breathing. Total work of breathing in this Campbell diagram is represented by the area contained within the pressure–volume loops. The recoil pressure (compliance) of the chest wall (Cw) is shown as the broken line with a positive gradient. At any given volume, the pressure generated by the respiratory muscles is the difference between Cw and the point on the pressure–volume loop. The dynamic compliance of the lung ($C_{L_{dyn}}$) is represented as the *broken line* between the points of zero flow (beginning and end of inspiration). At any given volume, the pressure required to overcome the elasticity of the respiratory system is the differences between $C_{L_{dyn}}$ and Cw. The *shaded areas* (vertical for normal lungs; horizontal for hyperinflated COPD lungs) represent the elastic work of breathing. *Unshaded areas* of the pressure–volume loops represent work to overcome airway resistance. Note how both elastic and resistive work increases in hyperinflated COPD lungs compared with normal lungs. IC = inspiratory capacity; TLC = total lung capacity.

In hyperinflated patients, tidal breathing occurs at higher volumes closer to the TLC, which represents a shift up the compliance curves. Compared with breathing at a lower volume, elastic work is increased at the beginning of inspiration and continues to increase as the volume of the lung increases during inspiration (Figure 4). These changes can have a marked effect on the total work of breathing, increasing demand on the respiratory muscles and placing them at risk for fatigue.

BRONCHODILATORS FOR THE TREATMENT OF HYPERINFLATION

Only a portion of patients consistently show significant responses to an acute dose of a bronchodilator in COPD, especially if response is defined by a change in FEV_1 and FEV_1/FVC ratio. In the past, this seemingly muted response to bronchodilators has been used to differentiate between COPD and asthma (reversibility testing) (8). The validity of this procedure is debatable, especially since airflow measures of reversibility vary widely over time and the degree of response to an acute dose of bronchodilator in patients with COPD is dependent on the degree of hyperinflation (9). Newton and coworkers retrospectively analyzed the responses of 957 patients to an acute dose of albuterol, according to their degree of hyperinflation, and found bronchodilator response, based on measures of both airflows and lung volumes (including RV, FRC, and IC), to be significantly greater in severely hyperinflated patients (9). This suggests that changes in airflow parameters may be more dependent on a reduction in hyperinflation than on an improvement in airway resistance. In other words, reducing hyperinflation and improving IC with a bronchodilator increases the maximum volume of air capable of being inhaled, thereby facilitating a larger and more forceful exhalation.

The same study also investigated the impact of using a definition of "bronchodilator response" based on changes in lung volumes independent of changes in airflows (9). Remarkably, the percentage of patients classified as responders increased from 33% for responses based solely on FEV_1, to 59% with inclusion of IC responses, to 76% with inclusion of responses to both IC and RV. This suggests that assessing the efficacy of bronchodilators in COPD by FEV_1 response alone greatly underestimates the benefits that may be achieved with these drugs.

Short-acting bronchodilators have been the classic therapy for COPD for many years, and continue to be recommended on an "as needed" basis (8). Although short-acting bronchodilators are effective for relief of transient episodes of hyperinflation, they are a less practical solution in cases where dynamic hyperinflation can be present at rest or during daily activities. In these cases, relief is continuously required throughout the day, when patients are active, as well as during the hours of sleep. Dosing with short-acting bronchodilators inevitably leads to a fluctuation of EELV as a dose is taken and then the effect wanes and does not continue through the night to the next morning.

One rationale behind the use of long-acting bronchodilators is to reduce EELV back toward the resting FRC volume for as much of a 24-h period as possible, an effect that could be termed pharmacologic lung volume reduction. Spikes of activity may still require additional dosing with a short-acting therapy; however, patients would generally breathe at volumes farther away from

any threshold associated with debilitating dynamic hyperinflation. Such therapy would be expected to increase exercise tolerance and, ultimately, quality of life. Tiotropium is the first 24-h long-acting bronchodilator (10) that provides the potential to achieve this goal with once-daily dosing. Significant reductions in parameters of hyperinflation (RV, FRC, and IC) achieved with tiotropium therapy are still present 24 h after a single daily dose in the morning (11, 12). This predose measurement is important, as the period before the next morning dose is not only when you would expect the least effect of the drug, but also coincides with a diurnal period of greatest risk for lung hyperinflation. Furthermore, parameters of hyperinflation with tiotropium therapy appear to improve over time, with greater reductions observed after 6 wk compared with after 3 wk in the same study (12). Whether pharmacologic lung volume reduction with once-daily tiotropium (and any other future drugs like it) in patients with COPD is of sufficient magnitude to eliminate the need for lung volume reduction surgery remains to be determined. Such therapy, however, offers the hope for a much less invasive means of ameliorating the effects of hyperinflation on respiratory mechanics and work of breathing in patients with COPD.

SUMMARY

Parameters of hyperinflation in patients with COPD may be more important than parameters of airflow in terms of patient functional activity and dyspnea. Hyperinflation in COPD occurs via both static and dynamic processes, which, although they share the same common pathologic foundation, occur by different mechanisms. Static hyperinflation is a minor contributor to hyperinflation in the majority of patients with COPD, and is caused by an increase in lung compliance due to emphysema. Dynamic hyperinflation is related to the degree of airflow limitation and time available for exhalation, both of which vary over time. Once hyperinflated, a patient's ability to breathe is significantly compromised due to mechanical restrictions resulting from a reduced IC, an increase in the work of breathing, and deleterious effects on inspiratory muscles and respiration. Collectively, these changes can impact clinical outcomes, including functional capacity, dyspnea, and exercise performance. Variability of dynamic hyperinflation offers the possibility for an intervention to slow or reverse the hyperinflation process.

Responses to bronchodilators have previously focused on measures of expiratory airflow. However, bronchodilators also have significant effects on lung volumes, even when effects on expiratory airflow seem small. Use of long-acting bronchodilators, such as tiotropium, can sustain significant improvements in hyperinflation in patients with COPD by mechanisms similar in effect to lung volume reduction surgery. It remains to be seen whether such long-acting bronchodilators will replace the need for surgery.

Conflict of Interest Statement: G.T.F. has worked as a consultant, participated on the Advisory Board, and been paid to speak at educational meetings for Boehringer Ingelheim and for GlaxoSmithKline. He has participated on Advisory Boards for Novartis and Schering Plough. He has received industry grant funding for research from Boehringer Ingelheim, GlaxoSmithKline, Emphasys, Abbott, Hoffman LaRoche, Centocor, and Oscient. He has received honoraria from Boehringer Ingelheim and Pfizer for his participation in this symposium. This article does not include discussion of "off-label" use.

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