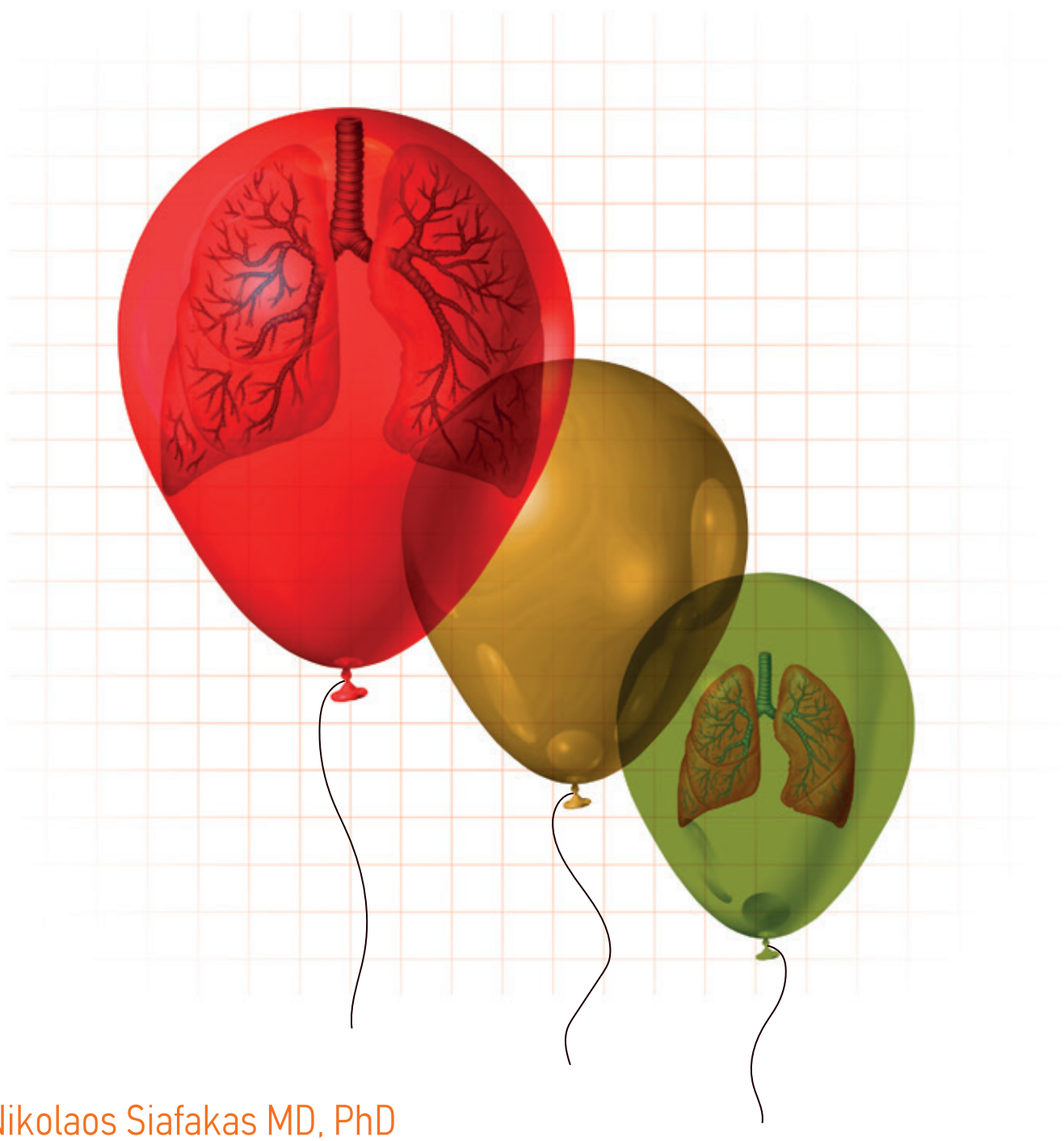
HYPERINFLATION OF THE LUNG AND ITS MANAGEMENT



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Foreword

In economic terms, Hyperinflation means a very high and accelerating inflation with a huge increase in commodity prices that are going out of control, and thus the local currency rapidly loses its value. Therefore, Hyperinflation is the nightmare scenario of any economy.

This book deals with Lung Hyperinflation a medical condition as catastrophic as hyperinflation is for the Economy.
It is well known, that Lung Hyperinflation in severe cases imposes a huge mechanical load on the respiratory system that may lead to respiratory failure with deadly cardiopulmonary consequences.
In addition, mild hyperinflation is a very common condition in Chronic Airway Diseases such as Chronic Obstructive Pulmonary Disease (COPD), Asthma, and Bronchiectasis, significantly affecting everyday symptoms and the Quality of life of those patients.
The aim of this book is to introduce the concept of Lung Hyperinflation, its effects on the mechanics of breathing leading to dyspnea, and its negative consequences for the functions of the Respiratory and Cardiovascular systems.
Since the book is for Practicing Pulmonologists, Internists, General Practitioners, Respiratory Physiotherapists, Nurses and Medical Students, specific efforts were made to avoid, as much as it was feasible, advanced physiology-pathophysiology, in other words - no algebra and no complex mathematical equations!
Major emphasis was put on the demonstration of a number of very effective modes of treatment for Lung Hyperinflation. Moreover, the authors repeatedly provide a compelling rationale (solidly based on mounting evidence) for lung deflation as the primary goal for the management of patients with Chronic Airways Diseases.
Thus, the main message of the book could be "Lung Hyperinflation is a very important clinical condition that makes breathing very difficult but today, a number of treatments can reverse it".
Finally, we wish to thank the Authors of the chapters for their excellent work and NOVARTIS HELLAS for supporting this project.

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Definition(s)

Nikolaos Siafakas

In simple terms lung hyperinflation means "Large" lungs but the accurate definition(s) needs measurements of Lung Volumes.
The practicing physician may suspect lung hyperinflation from the clinical examination or/and from the chest X-Rays.

Clinical Indications of Lung hyperinflation

Physical examination could reveal signs of lung Hyperinflation: High position of the shoulders (**Figure 1**), pursed lip breathing, forward leaning posture use of accessory muscles, "Barrel chest", tympanic sound on percussion and diminished breath sounds on auscultation, may indicate hyperinflation of the lungs. In addition, abnormal motion of the chest wall (Thoraco-abdominal dys-synchrony) or distortions (Hoover's sign) may be seen in hyperinflation.

Figure 1. *Patient with lung hyperinflation showing high position of his shoulders.*

Radiological finding of L.H.

X-Rays of the thorax could also show large lungs (**Figure 2**). There are two types of radiological findings of hyperinflation. The one of Emphysema (COPD) is with flat diaphragms, horizontal position of the ribs, small heart shadow, increased retrosternal airspace, attenuation of the blood vessels (**Figure 3**). The second type of X-Ray hyperinflation is that during an acute exacerbation of Asthma, the X-Rays shows similar signs as Emphysema but without any effect on the vessels or the parenchyma. However, the proper medical definition needs the Pulmonary Function Test laboratory and the measurements of Lung Volumes and Capacities.

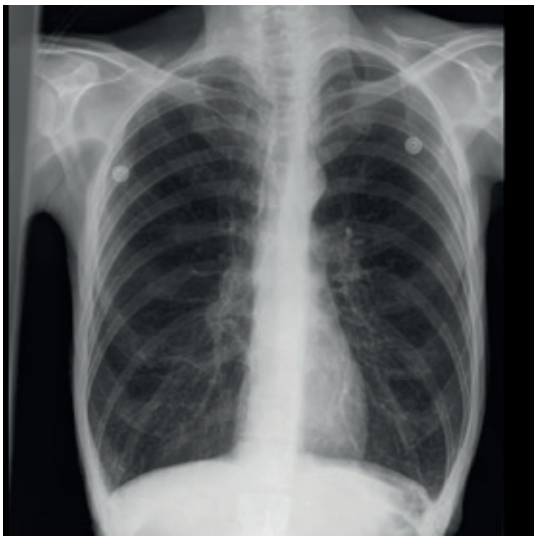

Figure 2. *X-Ray of the chest: Hyperinflation of the Lungs.*

Definition(s) / Nikolaos Siafakas

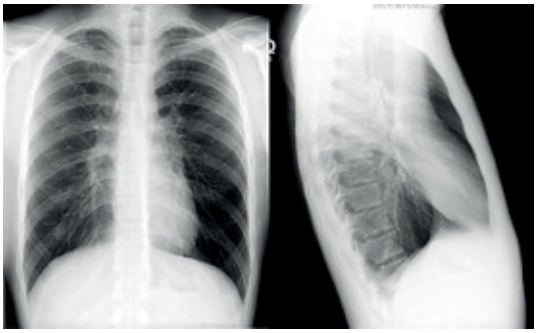

Figure 3.
PA and Lateral chest X-Rays showing radiological features of hyperinflation in Emphysema

Lung Hyperinflation:

1. Increase in End-Expiratory Lung Volume (EELV) that is the level of lung volume at the end of expiration. In other words, the increase in the Functional Residual Capacity (FRC)
2. An increase in Total Lung Capacity (TLC). More than 120% of predicted value and /or EELV, Residual Volume (RV), RV/TLC are increased and Inspiratory Capacity (IC)/ TLC is reduced. For educational purposes we may distinguish two types of lung hyperinflation,

a) STATIC (measured at steady state) *
b) DYNAMIC (measured during exercise)
c) or a combination of the two starting with STATIC and then adding a DYNAMIC component (**Figure 4**).

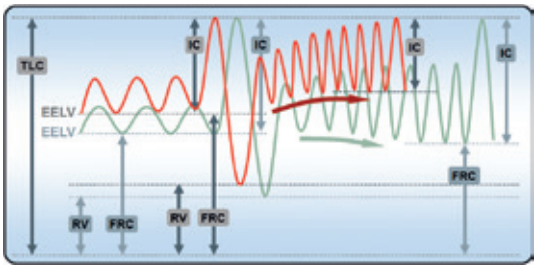

Figure 4. *Static and Dynamic Lung hyperinflation during exercise in a COPD patient (Red lines and symbols). Grey lines and symbols are of a normal subject similar condition. (Note that during exercise EELV decreases in the normal subject increasing IC. In contrast EELV increases in the COPD patient decreasing significantly the IC (Dynamic hyperinflation)*

Finally using lung volumes we may evaluate the severity of hyperinflation as mild, moderate and severe. (**Figure 5**).

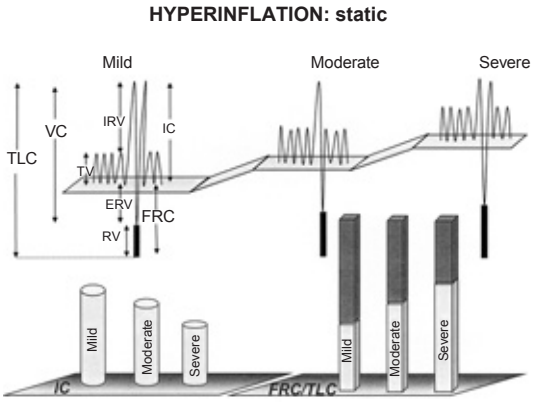

Figure 5. *Mild, Moderate and Severe levels of Static lung hyperinflation based on the measurements of the IC and / or of the FRC/TLC ratio.*

Suggested Reading

- G.J.Gibson: Pulmonary hyperinflation a clinical overview. Eur Respir J: 1996;9:2640-2649.

*Foot note: Even the measurement of Static hyperinflation at steady state conditions contain an element of Dynamic component. (For more details see Appendix)

HYPERINFLATION OF THE LUNG AND ITS MANAGEMENT

A.

PHYSIOLOGY

A1.
The Effects of Lung Hyperinflation on the Respiratory Muscles

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Dynamic Lung Hyperinflation

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A1.
The Effects of Lung Hyperinflation on the Respiratory Muscles

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PHYSIOLOGY

A1.
The Effects of Lung Hyperinflation on the Respiratory Muscles

Key Points

1.
The respiratory muscles are the only skeletal muscles that life depends on, since they are the vital part of the ventilatory pump.

2.
Hyperinflation significantly decreases the function of the respiratory muscles as pressure generators by changing their length and geometry and by altering the overall mechanics of breathing (area of apposition).

3.
The effect of increased radius of the diaphragm (Laplace's Law) is less important.

4.
Hyperinflation increases the work of breathing and the oxygen (O_2) consumption of the respiratory muscles.

5.
Hyperinflation has detrimental effects on the structure of the respiratory muscles.

6.
The respiratory muscles undergo significant adaptations during chronic hyperinflation to improve their function.

7.
The effects of hyperinflation on the respiratory muscles may lead to ventilatory failure.

PHYSIOLOGY

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The Effects of Lung Hyperinflation on the Respiratory Muscles

INTRODUCTION

It is well known that the act of breathing depends on the coordinated function of the brain, spinal cord, nerves, and respiratory muscles as parts of the vital ventilatory pump. The ventilatory pump consists of: a) the respiratory center(s) and the nerve supply of the respiratory muscles, b) two cavities: the thoracic and the abdominal, and c) the thoracic wall (rib cage, abdominal wall, and the diaphragm). The respiratory muscles are the important contractile part of the pump that maintain life. The respiratory muscles are the only skeletal muscles that life depends on and are the only ones that contract continuously through the whole lifespan. **Figure 1** shows the parts of the ventilator pump and the various pressure differences applied on them.

Respiratory Muscles and their nerves (Figure 2)

The respiratory muscles are divided into inspiratory and expiratory, primary and accessory.

Inspiratory muscles:

- Diaphragm
- External Intercostals
- Scalenes
- Sternocleidomastoids

Expiratory muscles:

- Abdominal muscles
- Internal intercostals

THE VENTILATORY PUMP

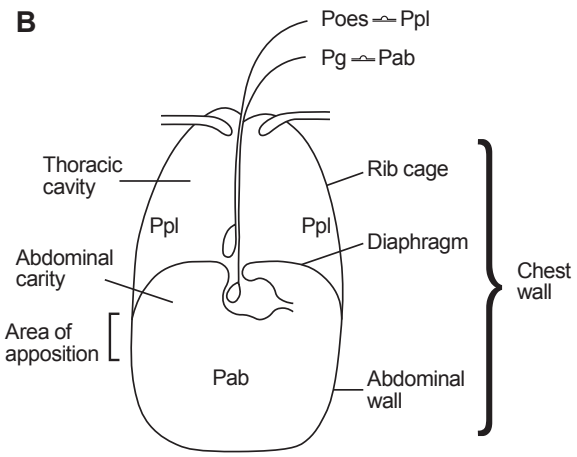
A

A. Respiratory centers (CNS) and nerves

B. Two Cavities
- B1) Thoracic
- B2) Abdominal

C. The Thoracic wall
- C1) Rib cage
- C2) Abdominal wall
- C2) Diaphragm

B



Pg - Poes = Pdi (= 0 at FRC)

Figure 1.

A. The components of the ventilatory pump.

B. The ventilatory pump, the pressures and the area of apposition (the lower part of the rib cage is driven by the abdominal pressure [Poes: Oesophageal; Pg: Gastric; Ppl: Plural; Pab: Abdominal; Pdi: Transdiaphragmatic)

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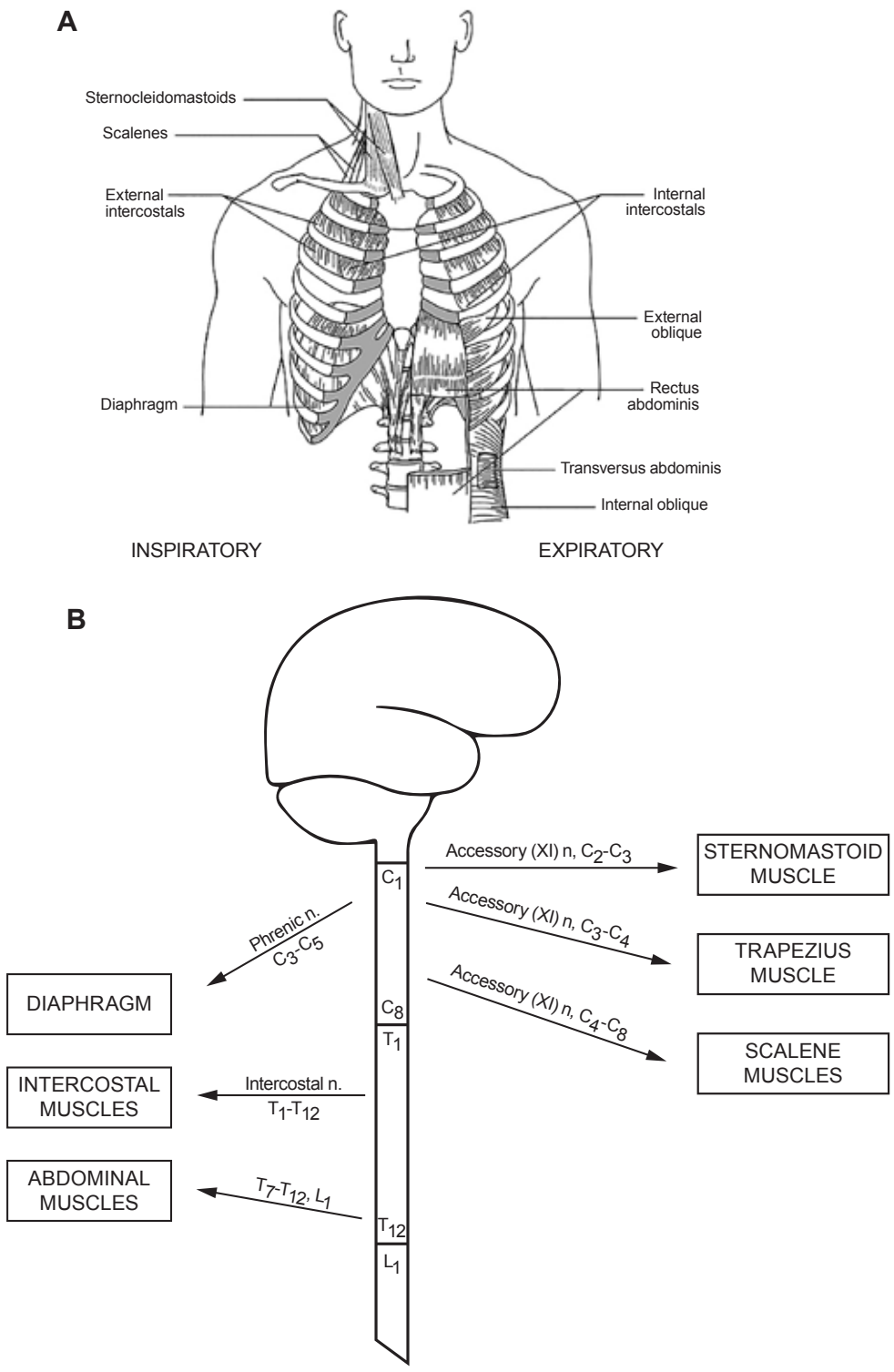

Figure 2.
A. The respiratory muscles (inspiratory - expiratory) *B. The innervations of the respiratory muscles.*

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Diaphragm

The diaphragm is the main muscle of respiration and primarily of inspiration. It has a dome-like shape, resembling a parachute (**Figure 3**). The diaphragm contracts via the neural pulse originating from the respiratory center(s) which is then conveyed via the spinal cord and the phrenic nerves. The roots of the phrenic nerves are of the C3, C4, C5 (**Figure 2B**). By contracting the diaphragm, the pressure in the abdomen increases, pushing the lower part of the ribs outwards, and thus increasing the volume of the thoracic cavity. This results in a decrease in the intrathoracic pressure; a development of a negative pressure gradient between the alveoli and the mouth which causes flow of air (inspiration) into the lungs.

Intercostals

These form the wall of the chest and are located between the ribs. The external intercostals lift the ribs and expand the transverse diameter of the thoracic cavity. The internal intercostals work in the opposite direction (expiration). Both are innervated by the thoracic nerves (T1-T12) (**Figure 2B**).

Scalene and Sternomastoid Muscles

These are considered accessory respiratory muscles and take part in respiration during critical conditions, such as respiratory failure (**Figure 2**) or when significant increases in ventilation are required, *e.g.*, exercise.

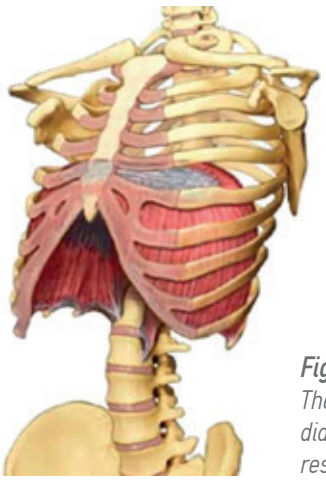

Figure 3.
The shape of the diaphragm that resembles a parachute.

Abdominal muscles

The abdominal muscles, and in particular, those that form the anterior abdominal wall (Rectus abdominis, transversus abdominis, internal / external oblique), are expiratory muscles, which are activated during forced expiration, coughing, and sneezing. In addition, the abdominal muscles act as stabilizers of the diaphragm. It is shown that the abdominal muscles are involved in maintaining the shape and length of the diaphragm in order to facilitate its efficiency to generate pressure.

In normal conditions, expiration is a quasi-passive phenomenon, depending on the relaxation of the inspiratory muscles and the elastic properties of the ventilatory pump.

Histology of the Respiratory Muscles

There are three types of skeletal muscle fibers:

- Type I or Slow (oxidative): High resistance to fatigue
- Type IIA or Fast (oxidative): Intermediate resistance to fatigue
- Type IIB or Fast (glucolytic): Low resistance to fatigue

The compositions of the respiratory muscles in health are approximately:

- 50-60% of Type I (slow)
- 20-25% of Type IIA (fast)
- 20-25%of Type IIB (fast)

*Structure of the Respiratory Muscles (**Figure 4**)*

The basic structure of the diaphragm or the other respiratory muscles is similar to that of any other striated (skeletal) muscle. The basic structure is the myofibril that contains the contractile element, the sarcomere

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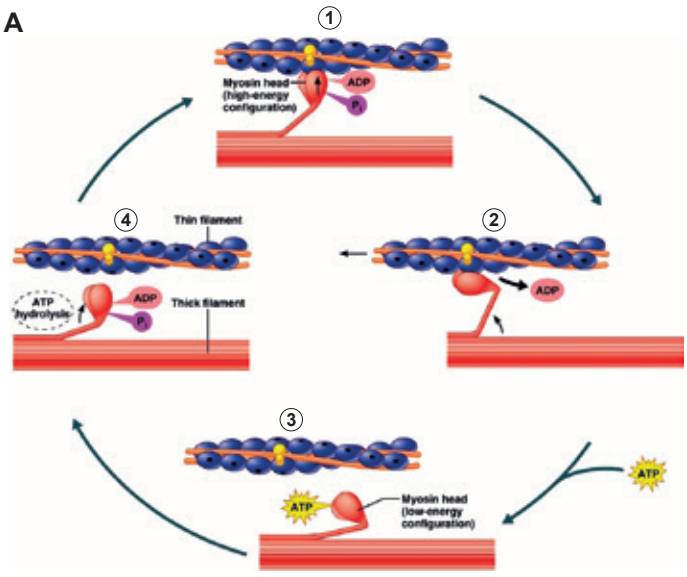
(**Figure 4A**). The sarcomere consists of a thick filament of Myosin and a thin filament of actin (**Figure 4A**). In accordance with the sliding concept of contracting, the force is developed by cross bridges where the myosin and the actin filaments overlap (**Figure 4A**). Myosin molecules have a long tail that ends in two heads with Adenosine triphosphate (ATP) binding sites. These heads link myosin and actin during contraction. Muscle contraction is a rather complicated procedure that needs ATP, calcium (Ca^2), magnesium (Mg^2), Anti-DNase B (ADB), troponin, tropomyosin and other elements to exist (**Figure 4B**). Finally, the neuromuscular junction is also involved in the initiation of the contraction (**Figure 4B**).



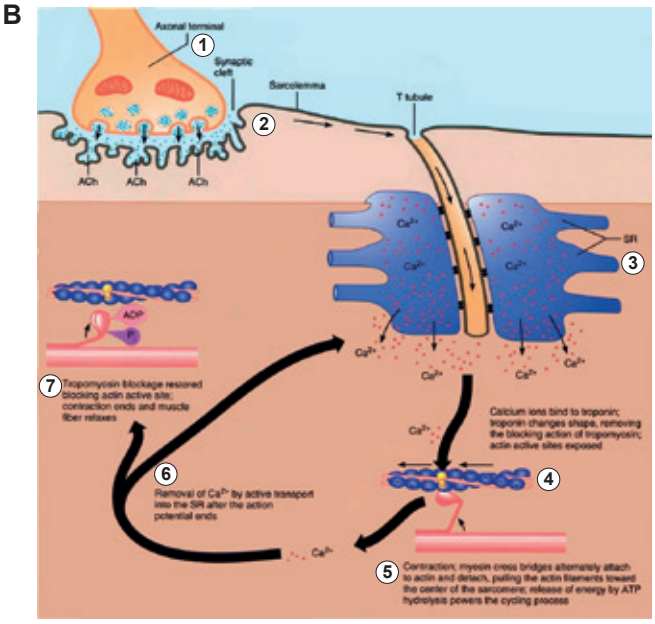


Figure 4.
A. Muscle fiber contraction.
The myosin-acting coupling and the role of ATP.
1. Myosin cross bridge attaches to the actin myofilament.
2. The myosin head pivots bends and pulls the actin filament (working stroke).
3. ATP attaches to the myosin head and the cross bridge is detached.
4. ATP splits into adenosine diphosphate (ADP) and inorganic phosphate (Pi) causing cock of the myosin head.

B. Neuromuscular coupling.
1. Release of Acetilocholine (Ach) from the nerve ending.
2. Action potential is travelling along the sarcolemma and T-tubules.
3. Release of calcium ions (Ca2+) from terminal systemic of sarcolemma.
4. Calcium bind to troponin.
5. Contraction (see Figure 4A).
6. Removal of Ca^2+ after action potential ends.
7. Contraction ends and fiber relaxes

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The Effects of Lung Hyperinflation on the Respiratory Muscles

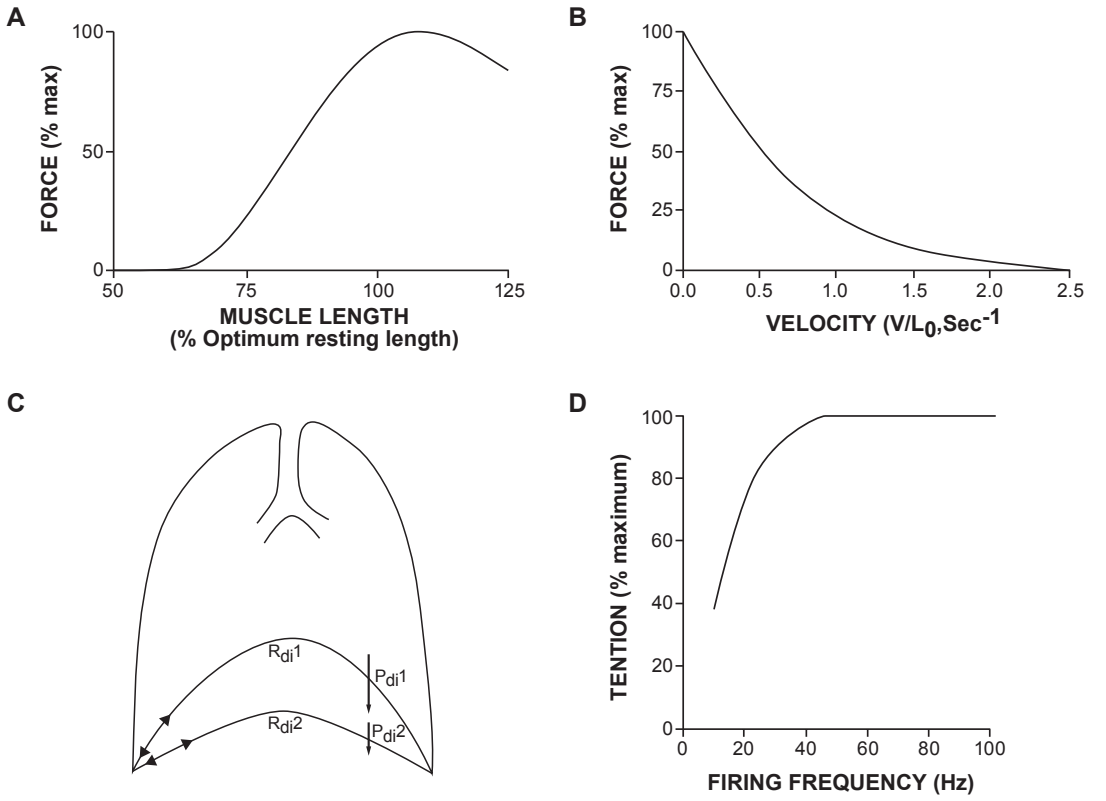

Figure 5. *The main physiological principles of the respiratory muscles.*
A. The length/force (tension) relationship (best at the 100% of the resting length).
B. The velocity/force relationship (best at lower velocity).
C. The shape of the diaphragm affecting its pressure generating capacity (Laplace's Law).
Pdi: Transdiaphragmatic pressure.
Rdi:The radius of the diaphragm.
Pdi1, Rdi1: Normal
Pdi2, Rdi2: Hyperinflation
Pdi1>Pdi2, Rdi1<Rdi2
D. The firing frequency/tension (force), which increases up to 40-60 Hz.

Physiology of Respiratory Muscles

The function of the respiratory muscles, as in all skeletal muscles, is depended on the general principal relationships of muscle function **Figure 5**:

a) The length/tension or force relationship.
b) The velocity/tension or force relationship.
c) The firing frequency/tension relationship.

In addition, due to the shape of the diaphragm, the curvature of the dome affects the radius; thus, the pressure generated (Laplace's Law) by the diaphragm (**Figure 5C**).

Figure 5A shows that there is an optimal resting length that generators figures the highest force. In addition, it is shown (**Figure 5B**) that as the velocity of shortening is increased, less force is produced. **Figure 5D** also demonstrates that above a certain firing frequency, the tension (force) produced by the muscle cannot be increased further. As we are going to discuss in more detail, the most important and detrimental effects of hyperinflation are primarily exerted on the diaphragm (*i.e.*, on the length/tension relationship, decrease of the area of apposition, changes in the geometry (orientation of the fibers), and to a lesser degree, by Laplace's law).

A1.
The Effects of Lung Hyperinflation on the Respiratory Muscles

The Effects of Hyperinflation on the Diaphragm

Length/tension relationship

Hyperinflation shortens the diaphragm and thus displaces it to a disadvantageous position of its length/tension curve. This results in a decrease in the power-generating capacity of the muscle. If hyperinflation becomes chronic, diaphragmatic function is adapted to the new hyperinflated state. This consists of changes in the structure of the muscle, especially by reducing the number of sarcomeres. On the other hand, if hyperinflation occurs acutely, as in an acute severe asthma attack, the shortening of the diaphragm may lead to acute compression of the T-tubules leading to reduce of action potential in the muscle. Thus, the operational length of the respiratory muscles is altered by hyperinflation decreasing its capacity to generate pressure (**Figure 5A, Figure 6**).

Area of Apposition

As shown in **Figure 6**, the contraction of the diaphragm increases the abdominal pressure that is exerted on the lower rib cage (the area of apposition), and results in the expansion of the lower part of the thorax. **Figure 6B** shows the position of the diaphragm in hyperinflation and its relationship with the area of apposition. It is obvious that this area is diminished or has disappeared in severe hyperinflation. This also has a significant effect in reducing the mechanical efficiency of the diaphragm.

Changes in Geometry

In hyperinflation, the diaphragmatic fibers at the insertion on the rib cage run transversally inwards and not cranially (**Figure 6B**). Thus, the diaphragm in severe hyperinflation becomes an expiratory muscle instead of been inspiratory. This change in geometry of the muscles may be the explanation of the Hoover sign in children. (see chapter B2)

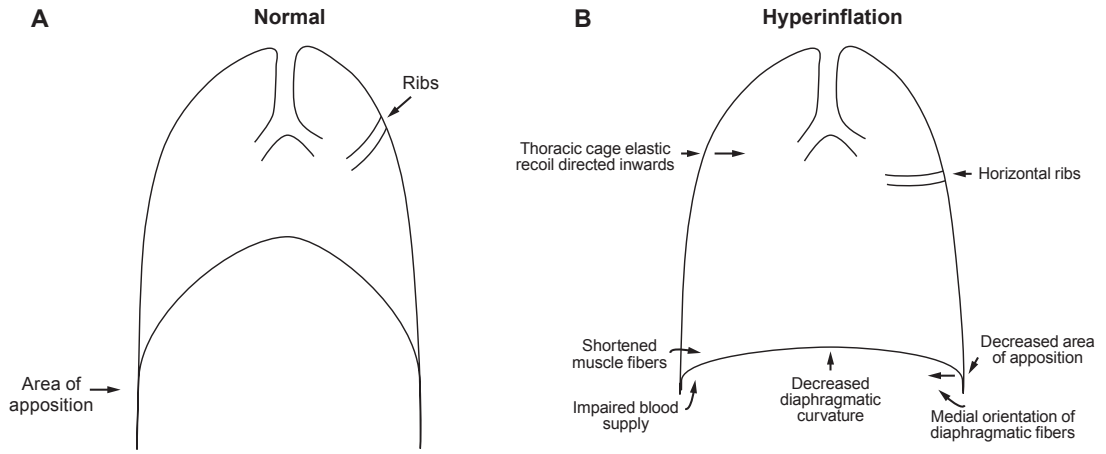

Figure 6. *Normal and hyperinflated respiratory system. A. Normal: Notice the area of apposition and the orientation of the ribs. B. Hyperinflation: Significant reduction of the area of apposition, shortening of muscles fibers, expiratory or medial orientation of fibers.*

A1.
The Effects of Lung Hyperinflation on the Respiratory Muscles

*Laplace's Law (**Figure 5C**)*
This law states that the pressure produced by the diaphragm is directly proportional to the tension developed and inversely proportional to the radius of curvature of the diaphragm. Since hyperinflation flattens the diaphragm (increases radius), it reduces its ability as a force-generating muscle. However, experimental observations have shown that geometrical changes are less important via Laplace's law.
In addition, hyperinflation of the lungs, which flattens the diaphragm, affects its blood flow due to compression of its blood vessels; consequently, this reduces the nutritional supply and oxygenation of the muscle.

Effects of Hyperinflation on the Intercostals
There is experimental evidence that hyperinflation profoundly affects the function of the internal and external intercostals muscles. In particular, hyperinflation affects the function of the most important part of the intercostals muscles: the parasternals. This is due to changes in the length/tension relationship and in geometry: in other words, the changes of the angle between the muscle fibers and the sternum.

Effects of Hyperinflation on the Other Respiratory Muscles
There are very few studies on the effect of hyperinflation on the sternomastoids and scalene muscles. These studies have shown a minimal effect on their function.

Effects of Hyperinflation on the Expiratory Muscles
In hyperinflation, the expiratory muscle activity is rather supportive of the diaphragm's function, by helping maintain the diaphragmatic shape and length. The action of the expiratory muscles contributes to the intrinsic positive end –expiratory pressure, altering the pressure-volume relation of the Respiratory System. (See chapter A2).

The structural changes
Finally, a number of cytological and molecular changes have been seen in the diaphragm of COPD patients with severe hyperinflation (**Figure 7**).

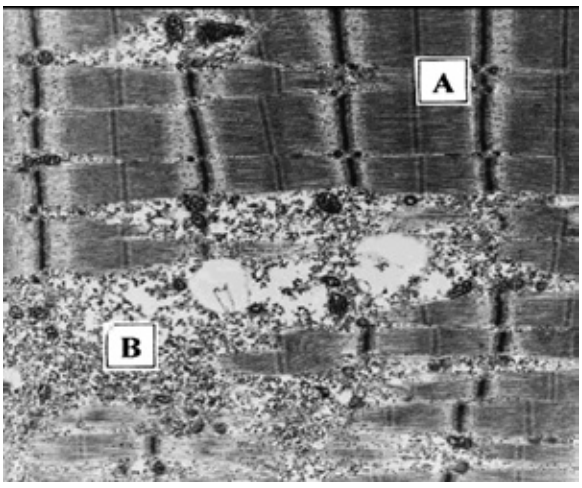

Figure 7. *Electromyographic photos of human, diaphragmatic sarcomeres.*
A. Normal.
B. Chronic obstructive pulmonary disease (COPD), showing extensive damage.

A1.
The Effects of Lung Hyperinflation on the Respiratory Muscles

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A2. Mechanisms and Consequences of Resting Lung Hyperinflation in Chronic Obstructive Pulmonary Disease

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PHYSIOLOGY

A2.
Mechanisms and Consequences of Resting Lung Hyperinflation in Chronic Obstructive Pulmonary Disease

Key Points

1.
Lung hyperinflation is common in chronic obstructive pulmonary disease (COPD) and occurs across the continuum of disease severity.

2.
Increased functional residual capacity (FRC) can occur in the absence of a significant increase in total lung capacity (TLC) and can indicate presence of expiratory flow limitation during resting breathing.

3.
Increased residual volume / total lung capacity (RV / TLC) ratio indicates pulmonary gas trapping and suggests peripheral airway dysfunction.

4.
Inspiratory capacity decreases linearly as forced expiratory volume in one second (FEV_1) worsens and is a simple indirect measure of increasing lung hyperinflation.

5.
The mechanical disadvantages of lung hyperinflation are partially offset by adaptations that preserve respiratory muscle strength and protect against fatigue.

6.
In situations where ventilatory demand increases, hyperinflation causes functional weakness of the diaphragm and ribcage muscles.

7.
Severe resting lung hyperinflation in the setting of a low inspiratory capacity greatly diminishes the ability to expand lung volume with each inspiration.

8.
Cardiac performance is impaired in the presence of hyperinflation as a result of reduced venous return, increased pulmonary vascular resistance, increased left ventricular afterload and external mechanical cardiac compression.

A2.
Mechanisms and Consequences of Resting Lung Hyperinflation in Chronic Obstructive Pulmonary Disease

INTRODUCTION

While expiratory flow limitation (EFL) is generally regarded as the pathophysiological hallmark of COPD, lung hyperinflation is a related and clinically important manifestation of the disease that deserves attention. Measures of resting lung hyperinflation have been shown to be predictive of respiratory and all-cause mortality and relate to dyspnea and exercise intolerance. In this chapter we will attempt to clarify definitions of lung hyperinflation, review causative mechanisms, consider the natural progression of hyperinflation in COPD, and briefly outline the negative consequences of lung hyperinflation.

Hyperinflation: Definitions and Determinants

In the absence of any consensus on the definition of lung hyperinflation, it is recommended when using this term to specify the volume compartment in question expressed as a percentage of the predicted normal value. For the purpose of this chapter, an increase in total lung capacity (TLC) (preferably measured by body plethysmography) exceeding either the upper limit of normal (ULN) or an empiric 120% of predicted, is consistent with the presence of *thoracic hyperinflation*. An increase in plethysmographic functional residual capacity (FRC) above either ULN or 120% of predicted is termed lung hyperinflation. An increase in plethysmographic RV exceeding either ULN or 120% of predicted is termed pulmonary gas trapping, also expressed by an increase in the RV/TLC ratio.

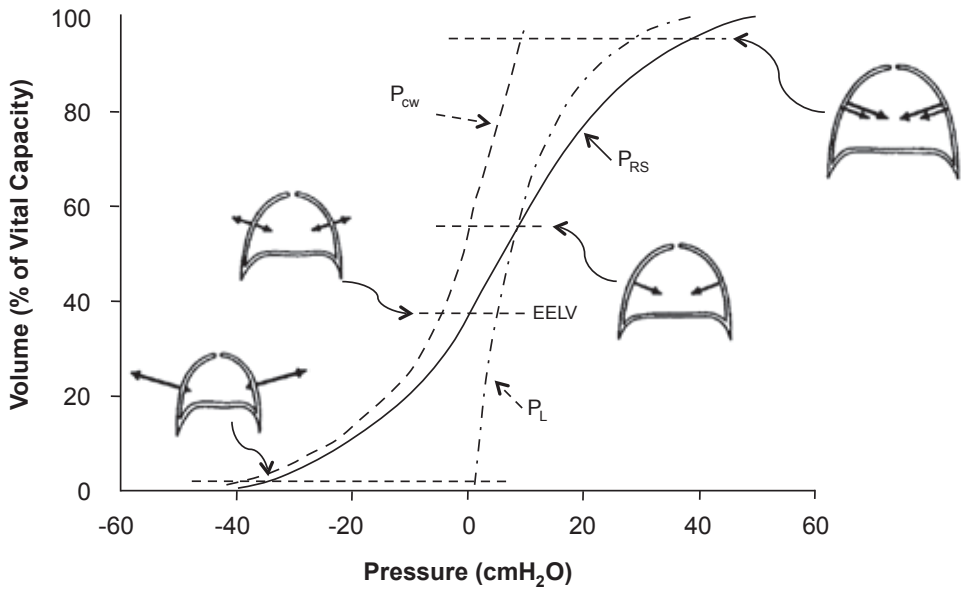

Figure 1. *Quasistatic V–P curves of lung (P_L), chest wall (P_{cw}), and total respiratory system (P_{rs}) during relaxation in a sitting position. The static forces of the lung and chest wall are indicated by the arrows in the drawings. P_L increases its curvature with increasing lung volume, whereas the opposite is true for the Pcw. Therefore, the fall in the compliance of the respiratory system at high lung volumes is mainly due to the decrease in compliance of the lung, whereas at low lung volumes it reflects decreased compliance of the chest wall. In the tidal volume range, the V–P relationships of both the lung and chest wall are nearly linear, and compliance of the lung and chest wall are about the same (approximately 4% vital capacity per 1 cm H_2O or 0.2 L/cm H_2O, in a seated position). The volume corresponding to each drawing is indicated by the horizontal broken lines. From: Agostini E, Mead J. Statics of the respiratory system. In: Fenn WO, Rahn H (Ed) Handbook of physiology. Respiration, Vol 1. Bethesda MD: American Physiological Society, 1964; 387-409.*

A2.
Mechanisms and Consequences of Resting Lung Hyperinflation in Chronic Obstructive Pulmonary Disease

Total Lung Capacity

Total lung capacity is the greatest volume of gas in the lungs after maximal voluntary inspiration. It depends on the static balance between the outward forces generated by inspiratory muscles during a maximal inspiratory effort and the inward elastic forces of the chest wall and lung (**Figure 1**). At TLC, these two sets of forces are equal and opposite in sign. The increase in TLC in COPD usually reflects the increased lung compliance due to emphysema.

Functional Residual Capacity at Rest

Functional residual capacity, or the lung volume at the end of quiet expiration during tidal breathing (*i.e.*, end-expiratory lung volume [EELV]) is increased in COPD compared with health. The term EELV is used interchangeably with FRC in the current chapter. FRC is not always synonymous with the static equilibrium volume of the relaxed respiratory system, *i.e.*, relaxation volume (V_r): the volume at which the elastic recoil pressures of lung and relaxed chest wall are equal and opposite in sign (**Figure 1**). Active or passive mechanisms often operate to make FRC different from V_r both in health and in COPD. For example, in healthy younger subjects during exercise, activation of expiratory muscles commonly drives FRC below the V_r.

Increase in FRC measured at rest has both static and dynamic determinants in COPD. Traditionally, increase in "static" FRC refers to increase in the V_r due to loss of lung recoil which resets the balance of forces between the lung and chest wall (**Figure 2**). Accordingly, the static V_r is higher than that of predicted

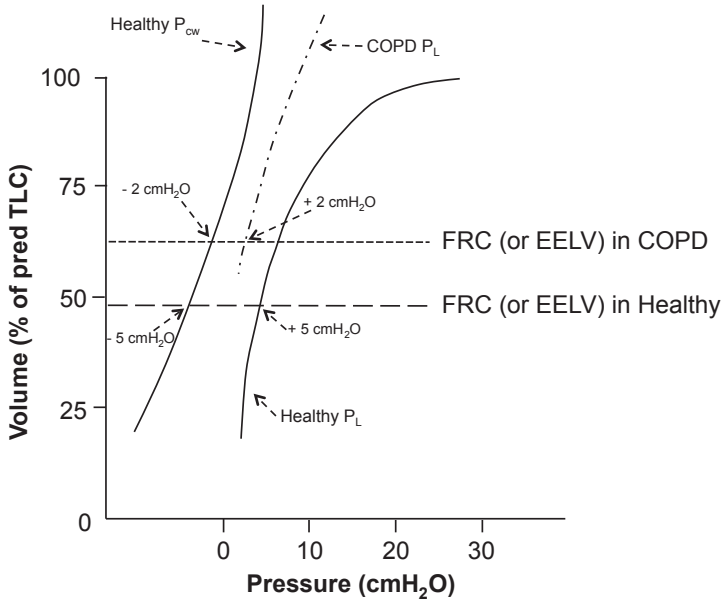

Figure 2. *Effect of reduced lung recoil pressure on functional residual capacity (FRC). Funtional residual capacity or end-expiratory lung volume (EELV) in the normal lung represents the volume at which the elastic recoil pressures of lung and relaxed chest wall are equal and opposite in sign, i.e., the net elastic recoil pressure of the total respiratory system equals zero (long-dashed lines). Loss of lung elasticity due to emphysema in COPD reduces lung recoil pressure; consequently, FRC occurs at a higher lung volume, which defines static hyperinflation (short-dashed lines). Under this circumstance, the elastic recoil pressures of lung and relaxed chest wall are equal and opposite in sign, meaning that the alveolar pressure is still atmospheric. TLC: total lung capacity. Modified from: Ferguson GT. Why does the lung hperinflate? Proc Am Thorac Soc 2006; 3(2): 176-179.*

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normal, and FRC (or EELV) is increased in COPD compared with health (**Figure 2**). The higher V_r means that the alveolar pressure at end-expiration remains atmospheric, *i.e.*, is still zero. Of note, "static" does not necessarily mean "at rest".

Resting FRC is dynamically determined. Lung hyperinflation is also influenced by body position and by body mass: for example, EELV decreases when adopting a supine position or with obesity. In this respect, FRC has been shown to decrease exponentially with increasing body mass index (BMI), with the largest changes occurring with BMI in the overweight to mild obesity range (**Figure 5**). Variable increases in EELV can also occur when minute ventilation (V'_E) is abruptly increased (*e.g.*, voluntarily, during anxiety/panic attacks, acute hypoxemia, or physical activity or during metronome pacing) or when EFL is suddenly worsened (*e.g.*, increased bronchospasm or during exacerbation). This acute increase in EELV is termed dynamic lung hyperinflation (DH) - the temporary and variable increase of EELV above the resting value.

Inspiratory Capacity

Inspiratory capacity (IC) is defined as the maximal volume of air that can be inspired after a quiet expiration to EELV. The resting IC (or IC/TLC ratio) is also used as an indirect measure of lung hyperinflation when TLC is stable. Resting IC progressively declines as airway obstruction worsens in COPD (**Figure 3**). Measurement of IC is motivation-dependent and is influenced by static strength of the inspiratory muscles and EELV. The IC represents the operating limits for tidal volume (V_T) expansion during exercise in patients with EFL and influences breathing pattern and peak ventilatory capacity (**see below**). The IC is diminished in the presence of significant inspiratory muscle weakness. Patients with a resting IC of <80% predicted are thought to have significant EFL during resting breathing and are at greater risk for developing DH during exercise.

Residual Volume

RV refers to the volume of gas remaining in the lungs after full exhalation, regardless of the lung volume at which exhalation is started. In young healthy adults, RV is determined by the balance between expiratory muscle force

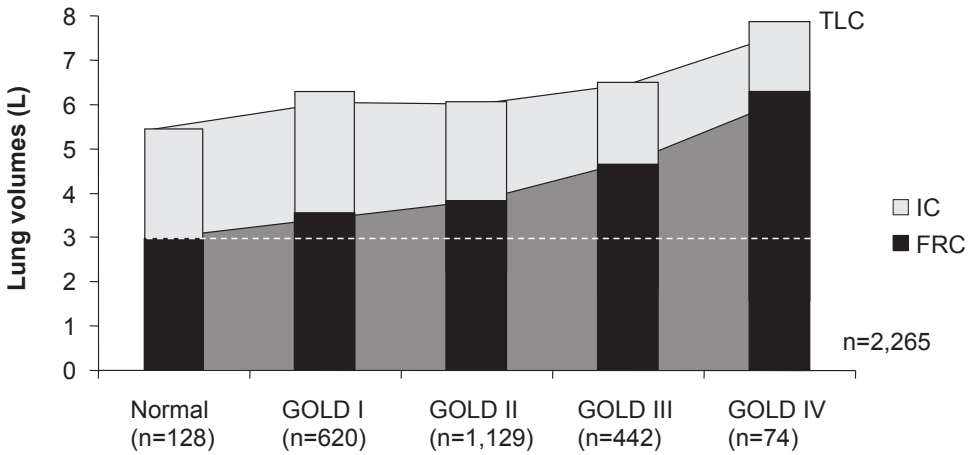

Figure 3. *Functional residual capacity (FRC) increases and inspiratory capacity (IC) decreases progressively across the GOLD stages (1, 2, 3/4) of COPD severity. GOLD: Global Initiative for Chronic Obstructive Lung Disease; TLC: total lung capacity. Constructed with data from: Deesomchok A, et al. COPD 2010; 7(6): 428-437.*

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and the outward elastic recoil of the chest wall (**Figure 1**). In older healthy adults, the normal loss of lung elasticity with age and associated decreases in maximum expiratory flow rate (premature airway closure and flow limitation) are associated with increased RV, compared to youth. In COPD, expiratory flow rates are very low near RV, and the ability to expire maximally may be influenced by limited breath-holding ability or breathlessness before expiration is "complete". The result is that RV can be higher than predicted. An increased RV/TLC reflects premature airway closure and pulmonary gas trapping, and is well documented in early or mild COPD even before FRC and TLC become increased.

The Natural History of Lung Hyperinflation

Insufficient data from longitudinal studies are available to allow us to chart the natural history of the development of lung hyperinflation in COPD. Clinical experience indicates that this is an insidious process that occurs over decades. It is acknowledged that such factors as genetic susceptibility, burden of tobacco smoke and frequency and severity of exacerbations collectively dictate the progression of hyperinflation. The 4-year UPLIFT® trial documented a mean rate of decline in pre-bronchodilator IC of 34 to 50 mL/year in patients with moderate to very severe COPD. In that study, the patients with the lowest baseline IC were those with the greatest rates of exacerbation and death. A recent cross-sectional study in 2265 patients found progressive increases in pulmonary gas trapping and lung hyperinflation (measured by RV and FRC) and a corresponding decline of IC across the continuum of COPD severity (**Figure 3**). Lung volume increases were shown to occur even in the earliest stages of COPD (*i.e.*, Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade 1) and increased with severity of airway obstruction (**Figures 3 and 4**). Another study showed that an increased BMI was associated with lower static lung volume

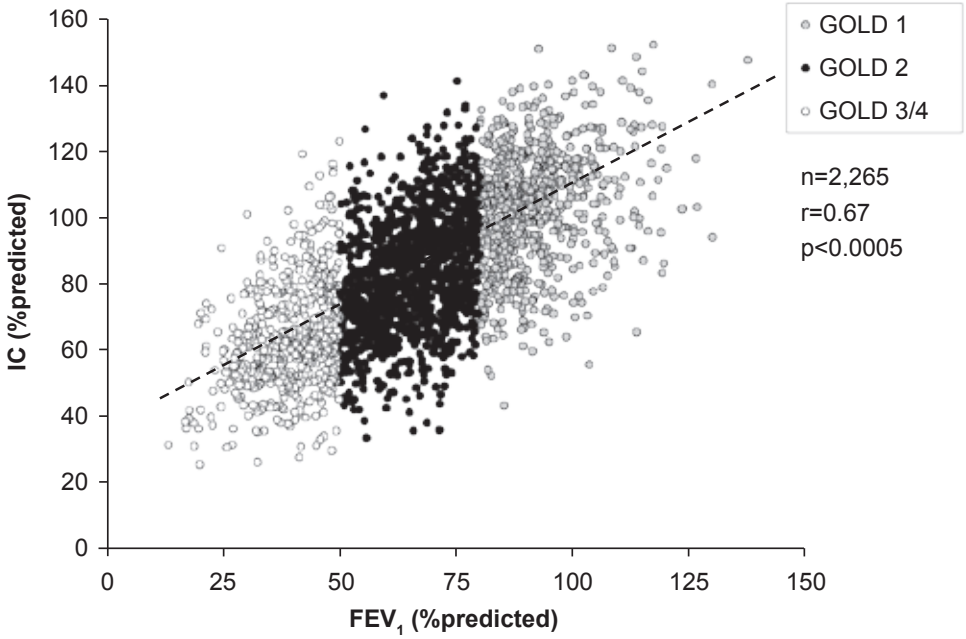

Figure 4. *Cross-sectional data showing that inspiratory capacity (IC) decreases linearly as the FEV_1 worsens in COPD (n=2,265). Constructed with data from: Deesomchok A, et al. COPD 2010; 7(6): 428-437.*

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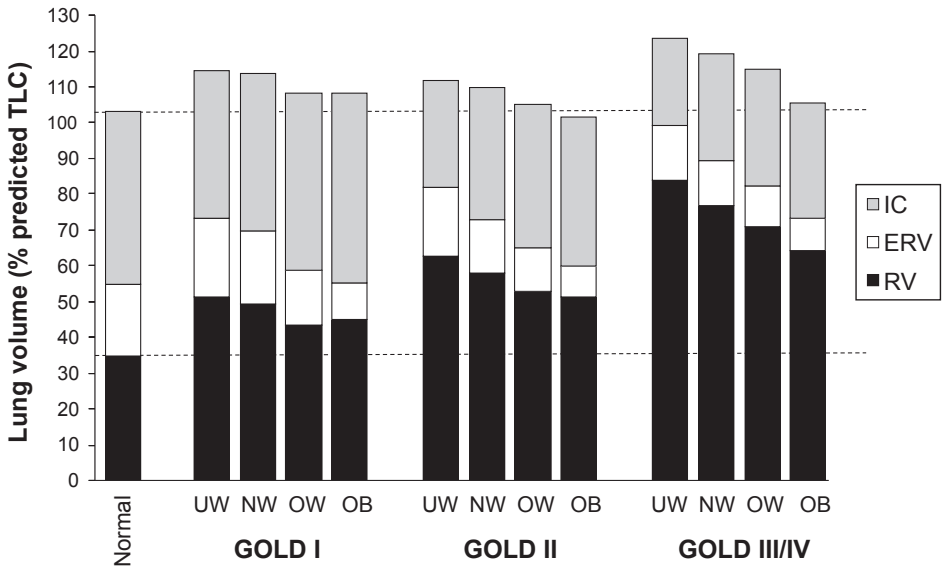

Figure 5. *Post-bronchodilator lung volume components are shown divided by GOLD stage and BMI. The Normal column represents measurements from an age-matched, healthy, non-smoker population. GOLD: Global Initiative for Chronic Obstructive Lung Disease; UW underweight (BMI 14-18.5 kg/m ^{2}); NW: normal weight (BMI 18.5-24.99 kg/m ^{2}); OW: overweight (BMI 25-29.99 kg/m ^{2}); OB: obese (BMI 30-55 kg/m ^{2}). From: O'Donnell DE, et al. Chest 2011; 140(2): 461-468.*

components, regardless of the severity of airway obstruction (**Figure 5**).

Hyperinflation across the Continuum of COPD

Small studies in mild COPD have reported increased static lung compliance, and quantitative computed tomography (CT) scans have shown emphysema and gas trapping. Gas trapping, as assessed by expiratory CT scans, can exist in the absence of structural emphysema and is believed to indirectly reflect small airway dysfunction in mild COPD. The presence of lung hyperinflation assessed by quantitative CT scans was found to predict a rapid annual decline in FEV_1 in smokers with a normal FEV_1. Corbin and coworkers, in a 4-year longitudinal study of smokers with chronic bronchitis, reported a progressive increase in lung compliance. Interestingly, these investigators reported that increases in TLC in milder COPD served to preserve slow vital capacity SVC and IC in the setting of increased RV and FRC, respectively. There is considerable heterogeneity in FRC and RV across GOLD grades, but many patients in each GOLD category have values that are above the predicted normal values. From cross-sectional studies, it would appear that RV and FRC increase exponentially as airway obstruction worsens.

Physiological Adaptations to Chronic Lung Hyperinflation

In the presence of lung hyperinflation, functional muscle weakness is mitigated, to some extent, by long term adaptations such as shortening of diaphragmatic sarcomeres and a decrease in sarcomere number, which cause a leftward shift of the length-tension relationship; thus, improving the ability of the muscles to generate force at higher lung volumes. In patients with chronic lung hyperinflation, adaptive alterations in muscle fiber composition (an increase in the relative proportion of slow-twitch, fatigue resistant, type I fibers) and oxidative capacity (an

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increase in mitochondrial concentration and efficiency of the electron transport chain) are believed to preserve the functional strength of the overburdened diaphragm and make it more resistant to fatigue. In this regard, Similowski *et al.* demonstrated that the reduction in the pressure-generating capacity of the inspiratory muscles of stable COPD patients was related to lung hyperinflation, but that diaphragmatic function in such patients was comparable to normal subjects when measurements were compared at the same lung volume. Despite these impressive temporal adaptations, the presence of severe lung hyperinflation means that ventilatory reserve in COPD is diminished and the ability to increase V'_E when the demand suddenly arises (exercise or exacerbation) is greatly limited.

Consequences of Resting Lung Hyperinflation

Increased EELV at rest is advantageous as it improves airway conductance and attenuates expiratory flow limitation to a variable degree. However, lung hyperinflation in moderate to severe COPD places the inspiratory muscles, especially the diaphragm, at a significant mechanical disadvantage by shortening its fibers, thereby compromising its force generating capacity by 30 to 55%. Lung hyperinflation also affects the capacity of the parasternal intercostals and scalenes to shorten with potential negative consequences. Known mechanisms of compromised diaphragmatic function include: 1) worsening of the length-tension relationship, 2) decrease in the area of apposition, 3) decrease in the curvature of the diaphragm, 4) change in the mechanical arrangement of costal and crural components of the diaphragm, and 5) increase in the elastic recoil of the thoracic cage.

Lung hyperinflation decreases the resting length of the diaphragm and, less so, the rib cage muscles. The shortening of the diaphragm is due to a decrease in the length of its area of apposition, which causes a decrease in its pressure generating capacity. At resting EELV, the curvature of the diaphragm is only 3.5% smaller in severe COPD patients than in healthy subjects. The radius of curvature also changes little over the range of IC in both severe COPD patients and healthy subjects. It follows that a change in the curvature of the diaphragm is likely to be less important than a change in length of diaphragmatic fibers in determining contractile force. The change in fiber orientation with lung hyperinflation decreases the ability of the diaphragm to generate force, and the diaphragm has an expiratory rather than inspiratory action on the rib cage.

When EELV becomes positioned above 70% of predicted TLC, thoracic elastic recoil is directed inward (*i.e.*, increased) so that the inspiratory muscles have to work, not only against intrinsic or auto- positive end-expiratory pressure (PEEPi) and the elastic recoil of the lungs, but also against the elastic recoil of the thoracic cage (**Figure 1**). The net effect is a pronounced increase in the work and oxygen (02) cost of breathing at rest in patients with severe COPD (reviewed in Loring).

Lung Hyperinflation and the Heart

Severe hyperinflation, as defined as an IC/TLC ratio <25%, has been shown to be associated with increased cardiovascular mortality, impaired LV filling determined by echocardiography, and reduced exercise tolerance. Severe lung hyperinflation has recently been linked to a reduced intra-thoracic blood volume and reduced LV end-diastolic volume as assessed by MRI. Barr *et al.* reported that in a large population-based sample of smokers and non-smokers, a 10% increase in the percentage of emphysema (measured by CT) correlated with reductions in left ventricular (LV) diastolic volume, stroke volume and cardiac output, as estimated by

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magnetic resonance imaging (MRI). Lung hyperinflation has the potential to impair cardiac function by increasing pulmonary vascular resistance. Increased intrathoracic pressure swings linked to the increased mechanical loading of hyperinflation may result in increased LV afterload as a result of the increased LV transmural pressure gradient (**Figure 6**). Reductions in venous return, right and left ventricular volumes, and LV stroke volume are additional consequences of the altered intra-thoracic pressure gradients.

Summary

In COPD, progressive EFL and alteration in the elastic properties of the lung are associated with the development of progressive lung hyperinflation and decline in the resting IC. Severity of lung hyperinflation is an independent predictor of mortality in COPD. A number of physiological adaptations partially preserve diaphragmatic function in the face of chronic hyperinflation. However, these adaptations are only partially effective and can become quickly overwhelmed when ventilatory demands increase, *e.g.,* during physical activity or during exacerbations. Severe hyperinflation is linked to increased threshold and elastic loading (and increased work of breathing) of the already weakened respiratory muscles. Moreover, the restrictive mechanical effects of a low IC limit the ability

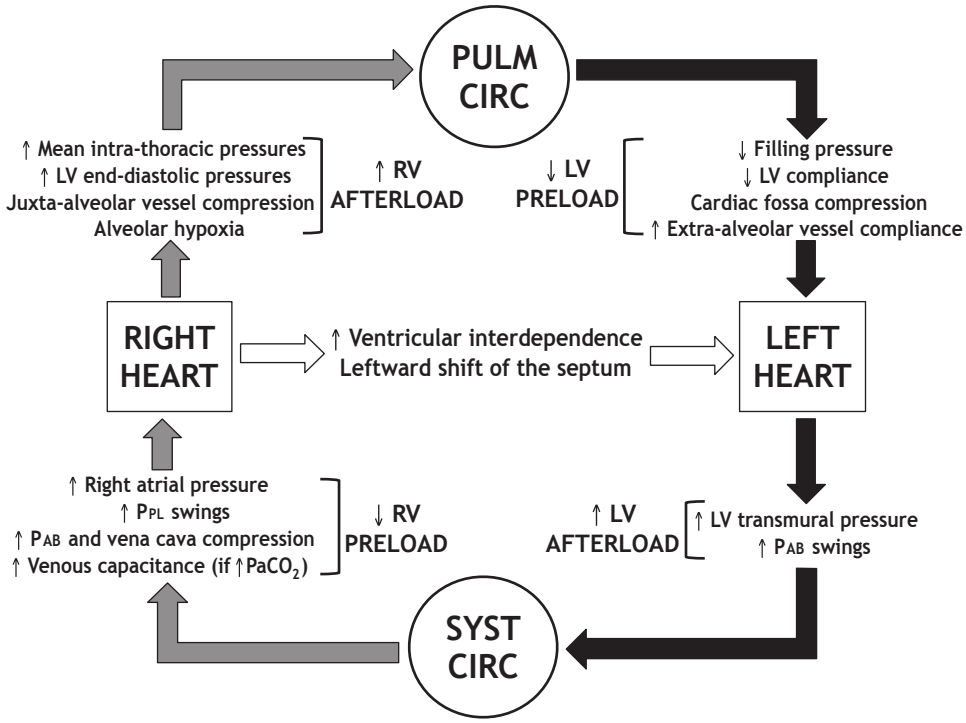

Figure 6. Schematic representation of the potential deleterious effects of lung hyperinflation on cardiopulmonary interactions in patients with COPD. Note that most of these interactions may vary according to phase alignment between the respiratory and cardiac cycles. Important modulating effects of volemic status, sympathetic nervous system activation, ventilation-related vagal reflexes and comorbidities (e.g., pulmonary hypertension and chronic heart failure) are not depicted. Circ: circulation; LV: left ventricular; Pab: abdominal pressure; $PaCO_2$: partial pressure of arterial carbon dioxide; Ppl: pleural pressure; Pulm: pulmonary; Syst: systemic; RV: right ventricular. From: Langer D, et al. Expert Rev Respir Med 2014; 8(6): 731-749.

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to appropriately increase tidal volume and ventilation when metabolic demand acutely increases. Lung hyperinflation also impedes cardiac performance, which in certain circumstances has important implications for oxygen delivery to the tissues.

Suggested Reading

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A3.
Dynamic Lung Hyperinflation

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PHYSIOLOGY

A3.
Dynamic Lung Hyperinflation

Key Points

1.
Dynamic hyperinflation (DH) is the temporary and variable increase in end-expiratory lung volume (EELV) above resting values in patients with airways obstruction.

2.
Dynamic hyperinflation is the product of worsening expiratory flow limitation and increased ventilatory demand.

3.
Progressive bronchoconstriction in acute asthma is associated with increasing DH which acutely loads the respiratory muscles and restricts tidal volume (V_T) expansion.

4.
During asthma attacks, DH introduces a widening disparity between the drive to breathe and the mechanical/muscular response of the respiratory system.

5.
Intensity of dyspnea during bronchoprovocation correlates well with the progressive reduction of inspiratory capacity and the increased ratio of respiratory effort to volume displacement.

6.
The impact of DH on respiratory muscle function (excessive loading and functional weakness) during acute exacerbations of COPD (AECOPD) depends on baseline respiratory mechanics and gas exchange abnormalities.

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7.
Attendant ventilation/perfusion abnormalities during AECOPD increase respiratory neural drive which amplifies DH, its negative cardio-respiratory sequelae and dyspnea perception.

8.
Recovery of dyspnea following AECOPD closely follows the gradual reduction in DH back to pre-exacerbation levels.

9.
Although exercise limitation in COPD is multifactorial, acute-on-chronic DH and its negative mechanical, cardio-circulatory and sensory consequences is centrally important in patients with more advanced COPD.

10.
The known negative effects of resting and dynamic hyperinflation provide a strong physiological rationale for the development of targeted interventions to deflate overinflated lungs in patients with chronic airflow limitation.

A3.
Dynamic Lung Hyperinflation

INTRODUCTION

Dynamic lung hyperinflation DH refers to the temporary and variable increase in end-expiratory lung volume (EELV) above the resting value in patients with obstructive airways disease. Dynamic hyperinflation occurs when expiratory flow limitation is abruptly increased during acute bronchospasm or exacerbation, often in a setting where minute ventilation (V'_E) is also acutely increased in response to increased respiratory neural drive. Depending on the extent of baseline lung hyperinflation, further DH can have important negative consequences for the function of both the respiratory and cardio-circulatory systems when the respiratory system is suddenly stressed. Moreover, acute DH is increasingly implicated as a major cause of dyspnea – the dominant symptom in patients with chronic airway diseases. In this chapter, we will briefly review the mechanisms and clinical consequences of DH during acute bronchoconstriction in asthma and exacerbation in COPD. Finally, we will summarize the role of DH in exercise limitation and dyspnea causation in COPD.

DH in Asthma

The main pathophysiological derangements in acute asthma are excessive airway narrowing/closure and lung hyperinflation. Acute DH occurs during bronchoconstriction because diffuse contraction of airway smooth muscle results in the non-uniform behavior of dynamic lung mechanics – many alveolar units develop delayed mechanical time constants for emptying. The increased airway resistance means delayed gas emptying as the expiratory time available during spontaneous breathing is not sufficient to allow EELV to decline to the normal resting relaxation volume of the respiratory system (V_r). In some instances, active "braking" of the inspiratory muscles

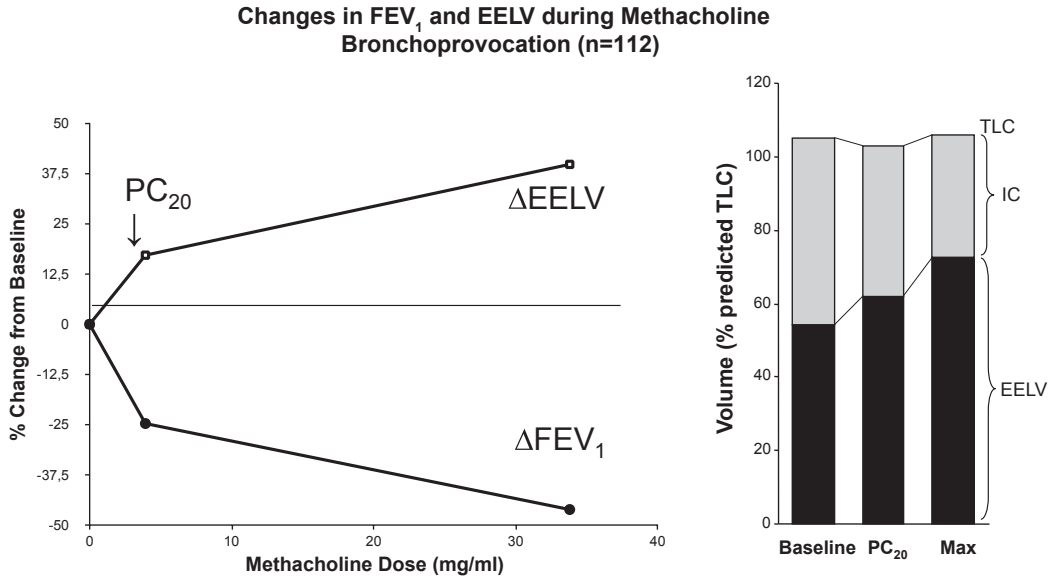

Figure 1. *Relationship between decreasing forced expired volume in 1 second (FEV_1) and inspiratory capacity (IC) during high-dose methacholine bronchoprovocation to a maximal response denoted by symptom limitation, a decrease in FEV_1 of 50% or more, or a maximum dose of 256 mg/mL (n=116). At the provocative concentration of methacholine causing a 20% fall in FEV_1 (PC20) and at the maximum response (46% fall in FEV_1), IC decreased by a mean of 0.62 L (22%predicted) and 1.06 L (37%predicted) from baseline, respectively. Data from Lougheed MD, et al. Chest 2006; 130: 1072-1081.*

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during expiration may assist in maintaining higher lung volumes to enhance expiratory flows, but this mechanism is disputed. It is well known that airway resistance drops at high lung volumes; thus, dynamic hyperinflation could be considered as a compensatory mechanism to reduce bronchoconstriction.

The fast decline of FEV_1 during progressive bronchospasm may simply reflect increased pulmonary gas trapping due to increased peripheral airway resistance. Accordingly, as residual volume (RV) and EELV increase, vital capacity (VC) and inspiratory capacity (IC) decrease. The reduced FEV_1, therefore, mirrors the increased RV/TLC ratio and reduced VC. Increased EELV occurs even at low levels of bronchoconstriction, and is discernible in many patients during methacholine challenge when $FEV_{1.0}$ has fallen by 20% of the baseline value (PC_{20}) (**Figure 1**). While hyperinflation serves to maximize tidal expiratory flow rates during bronchoconstriction because of the effect of alveolar-airway inter-dependence, the requirement of sustained breathing at high lung volumes ultimately has serious negative mechanical and sensory consequences. As a result of DH, tidal volume (V_T) comes closer to total lung capacity (TLC) and the upper non-linear "stiffer" extreme of the respiratory system's pressure-volume relationship, where there is significant elastic and inspiratory threshold loading of inspiratory muscles already burdened with increased resistive work. During acute bronchoconstriction, dynamic lung compliance is also decreased in association with the increased breathing frequency.

Acute thoracic hyperinflation adversely affects length-tension relationships of the inspiratory muscles, thereby compromising their ability to generate pressure. The net effect of this functional muscle weakness, coupled with excessive elastic and resistive loading, is that the inspiratory muscles are forced to utilize a large fraction of their maximal force generating capacity during spontaneous tidal breathing. As lung volume increases, the diaphragm is mechanically disadvantaged and scalene, sternomastoid and ribcage muscles are recruited. However, expiratory muscle recruitment is seldom prominent even during severe asthma attacks. A consequence of lung hyperinflation that is seldom emphasized is the severe mechanical constraints on V_T expansion: V_T represents a higher fraction of the progressively diminishing IC and inspiratory reserve volume (IRV) reaches its critical lower limit. Thus, thoracic volume displacement is greatly diminished, despite patients generating near maximal inspiratory efforts in response to increasing respiratory neural drive (RND).

In a study using high-dose methacholine challenge in patients with asthma, multiple regression analysis (where induced dyspnea was the dependent variable and several relevant mechanical parameters as independent variables) identified the decrease in IC (which reflects increased EELV) as the strongest contributor, explaining 74% of the variance in Borg dyspnea ratings (**Figure 2**). In qualitative terms, we established that dyspnea during acute bronchoconstriction is perceived primarily as inspiratory difficulty or unsatisfied inspiratory effort. Expiratory difficulty was less frequently reported, even when $FEV_{1.0}$ had fallen to 50% of the baseline value. We have proposed that perceived inspiratory difficulty arises when there is a disparity or mismatch between respiratory muscular effort (which approaches maximum) and the mechanical response of the system (which is greatly restricted due to thoracic hyperinflation). A strong statistical correlation between inspiratory

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Dynamic Lung Hyperinflation

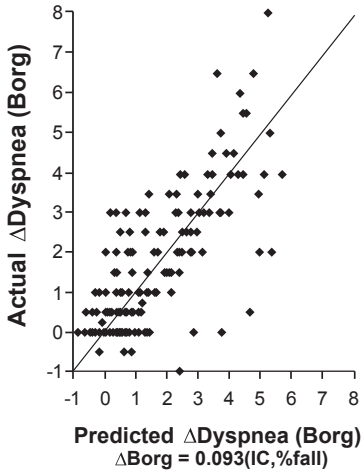

Figure 2. Change in end-expiratory lung volume, as measured by change in inspiratory capacity (IC), best predicted change in breathlessness (Borg scale) during induced bronchoconstriction in asthma (n=193 data points in n=21 subjects; p<0.001). From Lougheed MD, et al. Am Rev Respir Dis 1993; 148: 1452-1459.

difficulty and a crude index of neuromechanical dissociation (NMD) (*i.e.*, the ratio of esophageal pressure swings relative to maximum [esophageal pressure/maximum inspiratory value for Pes: Pes/PImax] to V_T/IC) supports this contention (**Figure 3**). In this context, the inspiratory threshold load imposed by DH at the onset of inspiration reflects the pressure that is isometrically generated by the inspiratory muscles to overcome the inward recoil of the lung and chest wall (in an expiratory direction) to initiate inspiratory flow. The finding that applied continuous positive airway pressure (CPAP) effectively relieves dyspnea by counterbalancing the effects of inspiratory threshold loading on the inspiratory muscles during provoked bronchoconstriction, further supports the notion that DH and respiratory sensation are mechanistically linked.

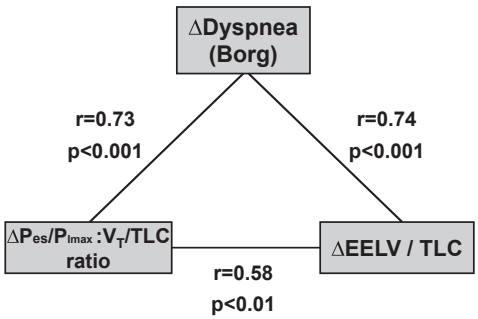

Figure 3. Significant interrelationships between perceived breathlessness, dynamic lung hyperinflation, and inspiratory effort standardized for tidal volume in subjects with mild asthma. From Lougheed MD, et al. Am Rev Respir Dis 1993; 148: 1452-1459.

DH during Exacerbations of COPD

The mechanisms of DH are broadly similar during induced bronchoconstriction in asthma and during exacerbations in patients with COPD. However, patients with COPD, especially those with more severe airway obstruction, are more likely to have significant baseline abnormalities of both lung mechanics and pulmonary gas exchange. Thus, the consequences of sudden acute-on-chronic DH in such individuals may be serious and even life-threatening. During AECOPD, airway resistance is abruptly increased due to a combination of bronchospasm, mucosal edema and sputum inspissation, which worsens expiratory flow limitation and compromises effective lung emptying as previously described. Furthermore, patients tend to adopt a rapid, shallow breathing pattern during an exacerbation, which further limits the time available for lung emptying; thus promoting greater DH in a vicious cycle. AECOPD differs fundamentally from experimentally provoked bronchoconstriction in asthma in that respiratory neural drive is more likely to be increased to a greater extent in the former. This response reflects increased

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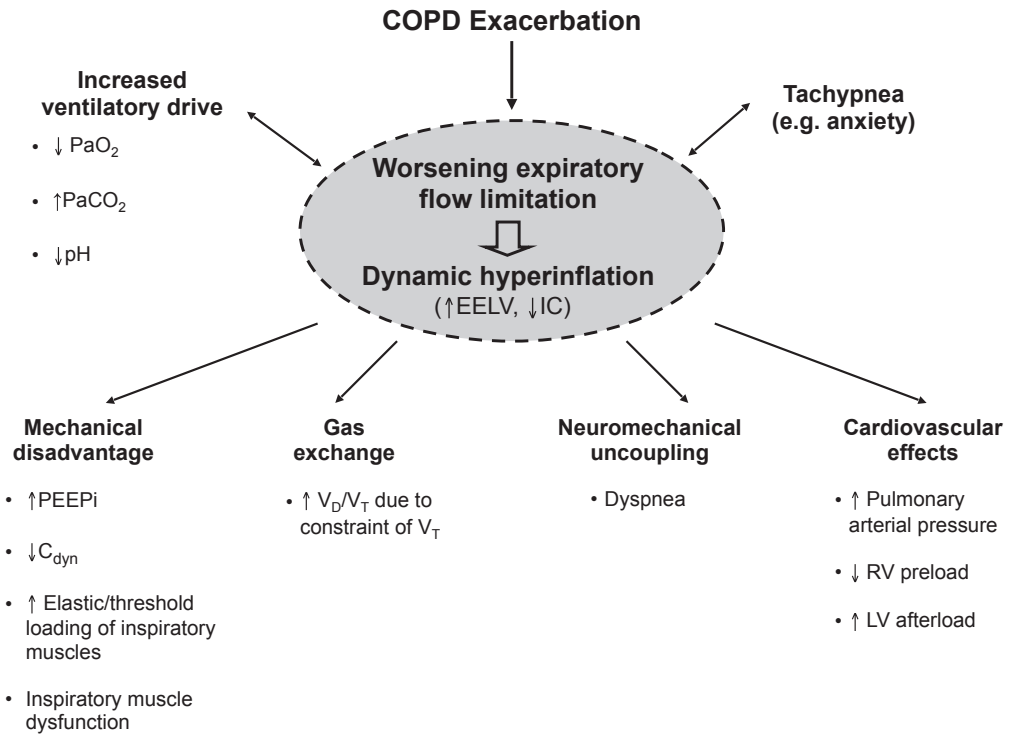

Figure 4. *Schematic of the negative consequences of dynamic hyperinflation during an acute exacerbation of COPD. Dynamic hyperinflation develops as a consequence of worsening expiratory flow limitation. EELV: end-expiratory lung volume; IC: inspiratory capacity; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; PEEPi: intrinsic positive end-expiratory pressure; Cdyn: dynamic compliance of the lung; V_D/V_T: physiological dead space; V_T: tidal volume; RV: right ventricular; LV: left ventricular. From O'Donnell DE, Parker CM. Thorax 2006; 61: 354-361.*

chemostimulation as a result of amplified ventilation-perfusion abnormalities. Moreover, subjective fear, anxiety or overt panic related to distressing dyspnea, with attendant increased sympathetic system activation, also powerfully influence breathing pattern to worsen DH. A summary of the deleterious effects of DH on respiratory and cardiac function (see below) during an AECOPD are presented in **Figure 4**.

During AECOPD, the respiratory muscles already burdened by increased resistive loading become subjected to increased elastic loading, decreased dynamic lung compliance and functional muscle weakness. Intrapulmonary pressures are positive at the end of expiration, representing intrinsic or auto- positive end-expiratory pressure ($PEEP_i$). $PEEP_i$ essentially acts as an inspiratory threshold load and may be as high as 6-9 cm H_2O during quiet breathing at rest in clinically stable patients with severe resting lung hyperinflation. During acute-on-chronic DH, PEEPi may rise precipitously and, together with the increased elastic (related to "high-end" mechanics) and resistive work, collectively increase the overall work and oxygen cost of breathing with development of fatigue or respiratory failure. During AECOPD, the mechanical output of the flow-limited and hyperinflated respiratory system may not increase in proportion to neural drive, resulting in critical neuromechanical dissociation of the respiratory system which may explain the worsening dyspnea (see below).

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Recovery from AECOPD

A study from our laboratory evaluated the changes occurring in various physiological parameters during recovery from a moderate AECOPD. Twenty patients with moderate to very severe COPD were studied within 72 hours of an AECOPD, and underwent full pulmonary function testing and symptom assessment using the dyspnea domain of the Chronic Respiratory Disease Questionnaire (CRQ-dyspnea). At the time of study entry (day 0), subjects were "very" short of breath (mean CRQ-dyspnea score = 2.4 units), and showed significant airflow obstruction (FEV_1 = 41% predicted) and hyperinflation (FRC = 164% predicted). At the end of the follow-up period (2 months), most patients reported that their dyspnea had returned to their pre-exacerbation level: mean CRQ-dyspnea score improved by 1.6 units. Indicators of hyperinflation and gas trapping also improved in parallel (**Figure 5**): at the final follow-up visit, FRC and RV had decreased by an average of 200 and 310 mL, respectively, and IC had increased by 300 mL. It is noteworthy that lung hyperinflation above baseline values persisted for approximately 2 weeks, on average, after initial presentation despite maximal medical therapy.

Dynamic Hyperinflation during Exercise in COPD

Dynamic increase in EELV is inevitable during exercise in patients with significant expiratory flow limitation in the setting of high ventilatory demand. Respiratory neural drive (and ventilatory demand) is often greatly increased in COPD because of the effect of increased wasted ventilation (high ventilation/perfusion ratios) and, in some instances, significant arterial hypoxemia and metabolic acidosis secondary to skeletal muscle deconditioning. In early exercise, mean inspiratory flow rates and tidal volume increase substantially, but expiratory time is often too short to allow complete gas emptying, resulting in DH. Increases in EELV above resting values by 0.3-0.6 L, on average, have been shown to occur in as many as 85% of patients with moderate-to-severe COPD during cycle exercise. In patients with advanced COPD, patterns of DH vary widely but the magnitude of increase in EELV is inversely related to the resting IC. Thus, in patients with a low resting IC due

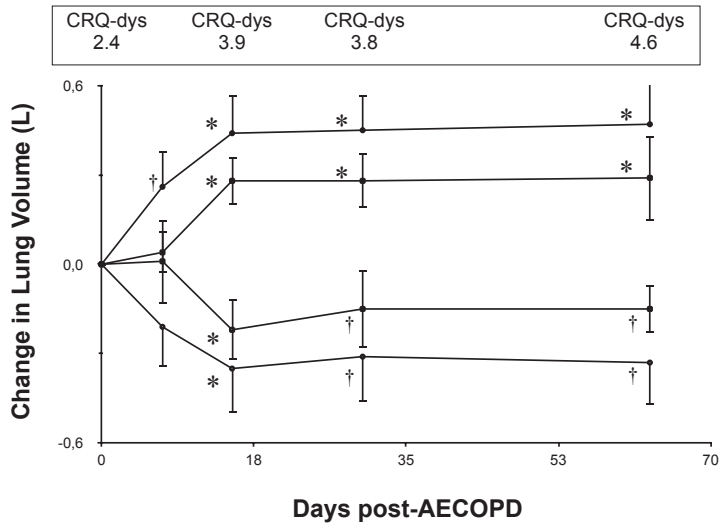

Figure 5. *Changes in lung volumes and mean Chronic Respiratory Disease Questionnaire (CRQ) dyspnea scores are shown during recovery from acute exacerbations of COPD (AECOPD) in patients that reached symptom-recovery during the ~2-month study period. SVC: slow vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume. Values are means ± SEM; *p<0.01, †p<0.05 significant difference from day 0. Modified from Parker CM, et al. Eur Respir J 2005; 26" 420-428.*

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Dynamic Lung Hyperinflation

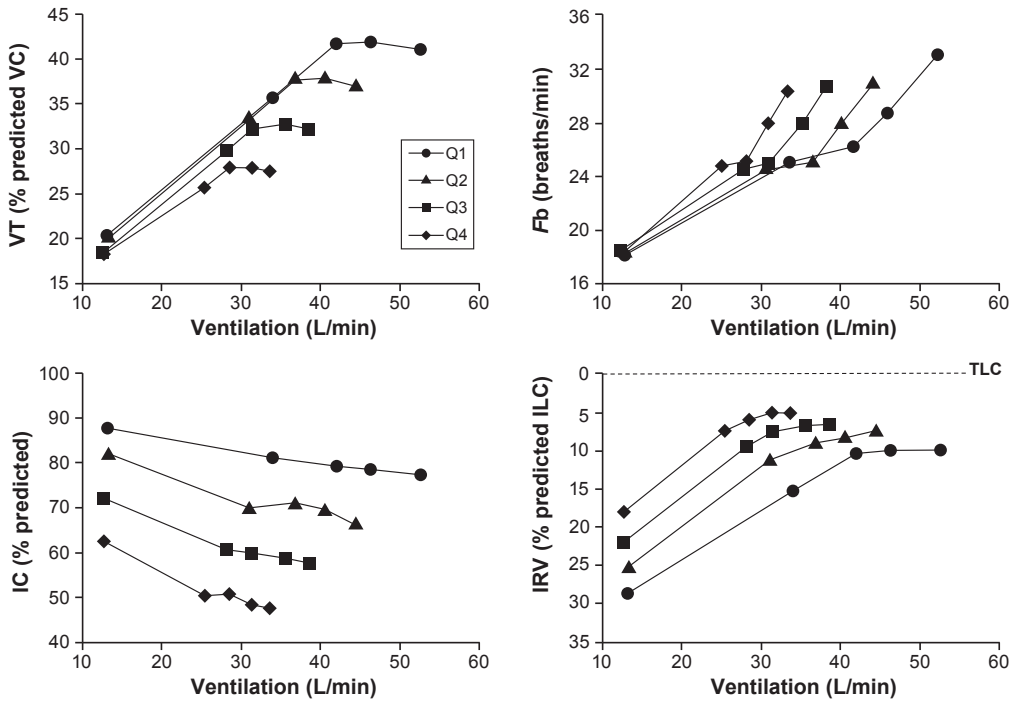

Figure 6. *Tidal volume (V_T), breathing frequency (F_b), dynamic inspiratory capacity (IC) and inspiratory reserve volume (IRV) are shown plotted against minute ventilation (V'_E) during high-intensity constant work rate exercise for each forced expiratory volume in 1 second (FEV_1, expressed as % predicted) quartile (Q). The upper through to the lower quartiles (Q1-Q4) represent the mildest to the most severe COPD groups, respectively. Note the clear inflection (plateau) in the V_T/V'_E relationship which coincides with an inflection in the IRV as end-inspiratory lung volume approaches total lung capacity (TLC). After this point, further increases in V'_E are accomplished by accelerating F_b. Data plotted are mean values at rest, isotime (2-min, 4-min), the V_T/V'_E inflection point and peak exercise. From O'Donnell DE, et al. Chest 2012; 141: 753-762.*

to severe resting hyperinflation, V_T quickly expands during exercise (even in the absence of DH) to reach a critical minimal IRV – a true mechanical limit where further increases in ventilation soon become impossible. Dynamic hyperinflation during exercise is even present in many individuals with mild airway obstruction (and dominant peripheral airways disease) as a result of the combined effects of higher ventilatory inefficiency and dynamic expiratory flow limitation. Dynamic hyperinflation occurs in the face of vigorous expiratory muscle effort and likely occurs "passively", rather than by active inspiratory muscle braking throughout the respiratory cycle.

Increasing lung hyperinflation as COPD progresses is associated with increasing reduction of the resting IC (**Figure 6**). During exercise when V_T reaches approximately 70% of the prevailing IC (or end-inspiratory lung volume reaches approximately 90% of the TLC at a minimal IRV), there is an inflection or plateau in the V_T/V'_E relation (**Figure 6**). This critical point represents a mechanical limit where further sustainable increases in V'_E are impossible in the face of near maximal respiratory neural drive. The inability to further expand V_T is associated with tachypnea – the only remaining strategy available in response to the increasing ventilatory drive. As explained above, increased breathing frequency results in further elastic loading due

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Dynamic Lung Hyperinflation

to DH and the increased velocity of shortening of the inspiratory muscles, with associated functional weakness and decreased dynamic lung compliance. In this setting, RND (indirectly assessed by diaphragm electromyography [EMGdi]) reaches >70% of the maximal possible value and tidal esophageal pressure swings increase to about 50-60 % of the maximal value. The work and O_2 cost of breathing required to achieve a given increase in $\dot{V}_E$ steadily increases to a high percentage of the total oxygen uptake. These collective derangements can predispose to critical inspiratory muscle functional weakness, fatigue or even overt respiratory failure with carbon dioxide (CO_2) retention.

Cardio-circulatory impairment

Dynamic hyperinflation adversely affects dynamic cardiac function, by contributing to pulmonary hypertension by reducing right ventricular pre-load (reduced venous return) and, in some cases, by increasing left ventricular afterload. In the absence of cardiac disease, cardiac output has been found to increase normally as a function of oxygen uptake during submaximal exercise in COPD, although stroke volume is generally smaller and heart rate correspondingly higher than in health. Of note, peak cardiac output reaches a lower maximal value during exercise in COPD, which may be due, in part, to abnormal ventilatory mechanics. Finally, it has recently been postulated that competition between the overworked ventilatory muscles and the active peripheral muscles for a reduced cardiac output may compromise blood flow and oxygen delivery to the latter, with negative consequences for exercise performance. However, the impact of dynamic lung hyperinflation on cardiac output and ventilatory/locomotor muscle competition during exercise needs further study.

Respiratory mechanical abnormalities and dyspnea

Dyspnea is a common symptom in patients with COPD across the continuum of the disease

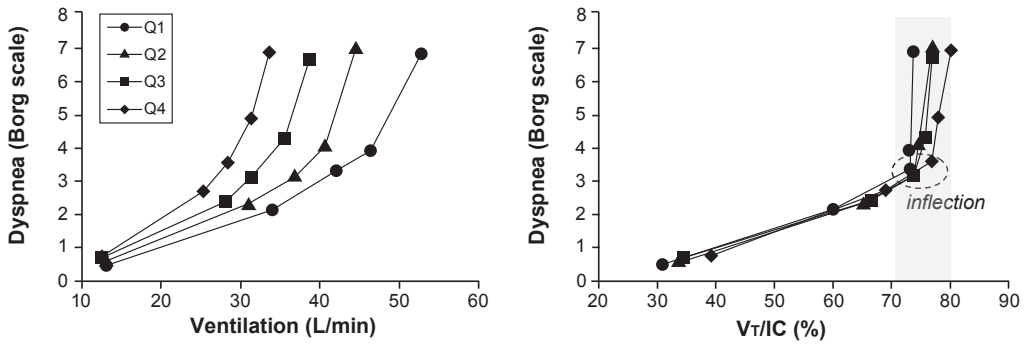

Figure 7. *Relationships between exertional dyspnea intensity and ventilation and the ratio of tidal volume to inspiratory capacity (V_T/IC) are shown during symptom-limited cycle exercise in COPD. There is a progressive increase in the dyspnea/ventilation curve with worsening disease. After the V_T/IC ratio plateaus (corresponding to the V_T inflection point), dyspnea rises steeply to intolerable levels. Quartiles (Q) of COPD severity are based on forced expiratory volume in 1 second (FEV_1) expressed as percent predicted (ranges: Q1 = 54.5–85.1; Q2 = 43.8–54.1; Q3 = 34.9–43.6; Q4 = 16.5–34.9). Data plotted are mean values at steady-state rest, isotime (i.e., 2 min, 4 min), the $V_T/\dot{V}_E$ inflection point and peak exercise. From O'Donnell DE, et al. Chest 2012; 141: 753-762.*

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and is often the proximate cause of exercise limitation. The increase in dyspnea intensity at any given ventilation as COPD severity increases (compared to health), reflects the progressively increasing intrinsic mechanical loading of the respiratory muscles (**Figure 7**). The rise in dyspnea intensity ratings during exercise correlates strongly with indirect indices of increased respiratory neural drive (central motor command output), such as tidal electromyographic activation of the diaphragm relative to maximum, tidal esophageal pressure swings relative to maximum and ventilation relative to peak ventilatory capacity. It is speculated that the amplitude of central neural drive (originating from motor cortical and medullary centers in the brain) to the respiratory muscles is sensed via neural interconnections (*i.e.,* central corollary discharge) between cortical motor and medullary centers in the brain and the somato-sensory cortex.

Dyspnea intensity is more closely correlated with the reduction in IRV during exercise than the change in EELV (*i.e.,* DH), per se. The V_T/V'_E inflection corresponds with the IRV/V'_E inflection during exercise and marks the point where dyspnea intensity sharply increases towards end-exercise; it also marks the point where the dominant descriptor of dyspnea selected by patients' changes from increased effort to unsatisfied inspiration. The V_T inflection represents the onset of a widening disparity between increasing central neural drive and the mechanical/muscular response of the respiratory system. In advanced COPD, the ratio of respired effort (and presumably neural drive) to V_T increases steeply from rest to peak exercise, reflecting progressive neuromechanical dissociation of the respiratory system. As in asthma during imposed acute DH, exertional dyspnea in COPD also closely correlates with indices of effort-volume displacement dissociation (*e.g.,* the ratio of Pes/PImax to V_T/IC). The consequence is that effective relief of dyspnea in COPD following bronchodilators (deflators) or lung volume reduction surgery are explained by partial restoration of effort-displacement ratios and reduced neuromechanical dissociation.

Summary

Dynamic hyperinflation occurs when expiratory flow limitation is acutely amplified during episodes of bronchoconstriction. It follows that DH is fundamental to the clinical expression of exacerbations of asthma and COPD. Dynamic hyperinflation in these clinical situations is often further compounded by the effects of concomitant increases in respiratory neural drive and ventilation. Similarly, during exercise in COPD the combined factors of worsening EFL, breathing pattern alterations and increasing respiratory neural drive dictate the pattern and extent of DH. The clinical consequences of DH in a given patient will depend on the baseline mechanical and gas exchange abnormalities that are present. In all of the above clinical situations, further reduction of the already diminished IC due to DH critically restricts V_T expansion, mechanically loads and weakens the inspiratory muscles, forces early respiratory mechanical limitation to exercise and compromises integrated respiratory and cardio-circulatory function. These critical mechanical and cardiac abnormalities can lead to profound functional respiratory muscle weakness, fatigue and even overt respiratory failure. Additionally, the growing disparity between increased respiratory neural drive and the blunted respiratory muscular/mechanical response after the V_T inflection is mechanistically linked to perceptions of respiratory discomfort and distress (dyspnea).

A3.
Dynamic Lung Hyperinflation

Suggested Reading

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A4. Measurement of Hyperinflation during Rest and Exercise

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Measurement of Hyperinflation during Rest and Exercise

Key Points

1.
The correct diagnosis of Lung Hyperinflation at rest and during exercise is highly dependent on the validity, reliability, and underlying assumptions of the tools used to measure lung volumes.

2.
Increases in functional residual capacity, residual lung volume, and total lung capacity relative to predicted values provide evidence of resting Lung Hyperinflation.

3.
Plethysmography, N_2 washout, and multiple breath inert gas dilution are three commonly used methods to measure functional residual capacity.

4.
N_2 washout and the inert gas dilution methods underestimate functional residual capacity and Hyperinflation, since they do not measure trapped gas in patients with obstructive lung diseases.

5.
The most common method of measuring Hyperinflation during exercise is to have patients perform inspiratory capacity maneuvers throughout exercise.

6.
Inspiratory capacity maneuvers are reliable even in large multicenter clinical trials.

7.
A comprehensive evaluation of ventilatory limitations during exercise can be achieved through flow-volume loop analysis and operating lung volume plots. These approaches are dependent on the accurate measurement of inspiratory capacity throughout exercise.

A4.
Measurement of Hyperinflation during Rest and Exercise

INTRODUCTION

The accurate diagnosis of Lung Hyperinflation (LH) at rest and during exercise is critically dependent on the measurement techniques used to assess lung volumes. It is important for the clinician to have a comprehensive understanding of the various lung volume components and their physiological determinants in order to appropriately classify a patient as having static or dynamic Hyperinflation. Recognizing the limitations of various measurement techniques is equally important for the correct interpretation of LH. Accordingly, the purpose of this chapter is to review the lung volumes and capacities used to assess Hyperinflation and to provide a general overview of the various methods used to quantify LH at rest and particularly during exercise.

There is no universal definition of LH, but it is generally accepted that Hyperinflation is characterized by an increase in total lung capacity (TLC), residual volume (RV), and functional residual capacity (FRC) relative to predicted normal values and/or an increase in the ratio between these variables (*e.g.*, RV/TLC, FRC/TLC). A firm cut-off has not been established, but values exceeding 120-130% predicted usually indicate clinically significant Hyperinflation.

Lung Volumes and Capacities

Figure 1 provides a schematic representation of lung volumes and capacities using a volume-time spirogram. There are four volumes including the tidal volume (V_T), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), and residual volume (RV). Capacities are derived from two or more of these lung volumes and include the functional residual capacity (FRC), inspiratory capacity (IC), vital capacity (VC), and total lung capacity (TLC).

The volume of air on inspiration and expiration during normal quiet breathing is the V_T. The maximum volume of air that can be inspired from the end of a tidal inspiration is the IRV. The maximum volume of air that can be expired from the end of tidal expiration is the

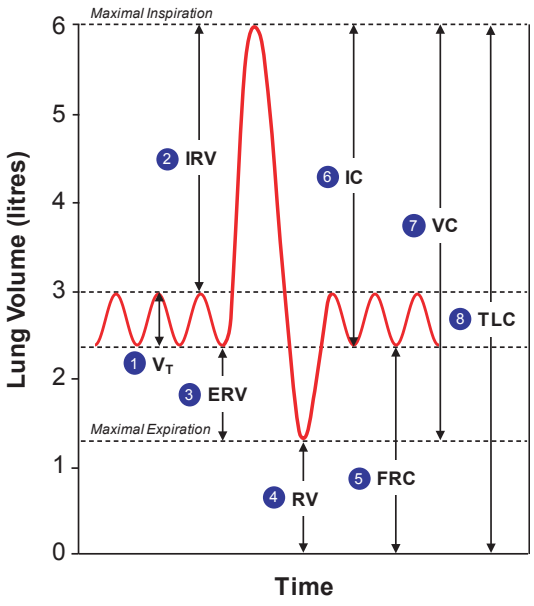

Figure 1. *Volume time plot showing different lung volumes and capacities. V_T: tidal volume; IRV: inspiratory reserve volume; ERV: expiratory reserve volume; RV: residual volume; FRC: functional residual capacity; IC: inspiratory capacity; VC: vital capacity; TLC: total lung capacity.*

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ERV. The volume of air remaining in the lungs after maximum expiration is the RV. Functional residual capacity refers to the volume of air remaining in the lungs at the end of tidal expiration (*i.e.,* the sum of ERV and RV) and is often referred to as the end expiratory lung volume (EELV). The maximum volume of air that can be inspired from FRC is the IC whereas the volume of air expired from full inspiration to full expiration is the VC. Finally, TLC is the volume of air in the lungs when the lungs are maximally filled (*i.e.,* sum of all volume components). Many of these volumes and capacities can be obtained from a spirometer, but the most important indices of LH (*i.e.,* TLC, FRC, and RV) require more sophisticated measurement techniques, as described below.

Determinants of FRC, TLC, and RV

Specific determinants of absolute lung volumes have been detailed previously (see recommended reading). Briefly, static FRC is determined by the balance between the inward elastic recoil forces of the lungs and the outward elastic recoil forces of the chest wall. Total lung capacity is determined by the balance between the inward elastic recoil forces of the respiratory system (primarily the lungs) and the outward forces of the inspiratory muscles generated during maximal inspiration. Residual volume is determined statically by the balance between the elastic recoil forces of the respiratory system (primarily chest wall) and expiratory muscle forces, at least in young healthy adults. In older adults and particularly in those with obstructive lung disease, RV is determined by "dynamic" mechanisms as described in other sections of this book.

Measurement of FRC

Ultimately, the goal when quantifying Hyperinflation is to measure FRC, because TLC and RV can simply be derived from FRC and the two components of VC (*i.e.,* IC and ERV). The methods used to measure FRC include body plethysmography (FRC_{pleth}), nitrogen washout (FRC_{N_2})and inert (helium) gas dilution (FRC_{He}); all of which have inherent limitations that can influence the interpretation and diagnosis of LH. The decision to use a specific method depends on a number of factors, including cost, availability of equipment and the patient population being studied. As such, it is important to clearly specify which method is used when reporting FRC values (*e.g.,* FRC_{pleth}, FRC_{N_2}, FRC_{He}). This chapter will provide a brief overview of the theory surrounding each measurement technique and the potential drawbacks that should be considered when interpreting LH. Lung volumes and Hyperinflation can also be assessed using conventional radiographs, computed tomography (CT), and magnetic resonance imaging (MRI). However, due to the lack of standardization and the limited published data, the American Thoracic Society/European Respiratory Society (ATS/ERS) does not make specific recommendations on the most appropriate imaging modality for measuring lung volumes. As such, imaging methods will not be discussed further in this chapter.

Body Plethysmography

Body plethysmography measures the volume of gas within the thorax and is the gold standard method for measuring FRC. This method requires the patient to sit inside of a sealed, rigid-walled body plethysmograph, or "body box". The patient breathes normally for several breaths and then pants against a closed shutter. The change in pressure in the

A4. Measurement of Hyperinflation during Rest and Exercise

lungs is measured at the mouth via a pressure transducer and is plotted against the change in thoracic volume as estimated by changes in body box volume. How the body box volume is measured depends on the type of body box used (*e.g.,* volume-displacement box, variable pressure box and flow box). Functional residual capacity is then determined using Boyle's law, which states that the volume of gas at a constant temperature is inversely related to the pressure applied to it. Plethysmography or thoracic gas volume (TGV) is calculated as follows:

$$TGV = -(\Delta V/\Delta P) \times Pb$$

where $\Delta V/\Delta P$ is the slope of body box volume and alveolar pressure line during panting and Pb is barometric pressure in cmH_2O (less water vapor).

Body plethysmography includes both ventilated and non-ventilated lung regions resulting in higher FRC values compared with other methods; particularly in those with obstructive lung diseases. Overestimation of FRC with body plethysmography can be minimized by using a lower panting frequency (≤ 1 Hz) and minimizing the compliance of the extrathoracic airway by having patients support their cheeks during panting. Despite these strategies, plethysmography may still overestimate FRC in those with severe airflow limitation. Nevertheless, body plethysmography remains the method of choice when assessing LH, particularly in those with obstructive lung conditions. Other disadvantages of this technique relative to other methods are that it is expensive and it requires patient cooperation.

Nitrogen (N_2) Washout

The multiple breath open-circuit N_2 washout method is based on the removal (*i.e.,* washing out) of N_2 gas from the lungs by having the patient breathe 100% O_2 for several minutes. The patient is asked to breathe normally at rest on the mouthpiece for approximately 30-60 seconds to become familiar with the breathing apparatus and to ensure stability of FRC. The patient is then switched from breathing room air to 100% O_2. The concentration of N_2 is then monitored during the washout phase. The test is terminated when the concentration of N_2 decreases below 1.5% for three consecutive breaths or if a leak is detected. FRC_{N_2} is calculated as follows:

$$FRC_{N_2} = \frac{(\text{volume } N_2 \text{ washed out}) - (N_2 \text{ tissue excretion})}{\text{initial} - \text{final lung } N_2 \text{ concentration}}$$

where N_2 tissue excretion is estimated using a standard prediction equation.

FRC measured using N_2 washout generally agrees well with plethysmography and other methods (*e.g.,* gas dilution and imaging), at least in healthy adults. However, this technique is limited for the assessment of LH in patients with respiratory diseases because it only measures well ventilated regions of the lungs. This methodological limitation has been shown to cause an underestimation of FRC compared with plethysmography. Thus, caution is warranted when making a diagnosis of LH using this method, particularly in patients with respiratory conditions that are typically associated with gas trapping.

Multiple Breath Inert Gas Dilution

The inert gas dilution method measures FRC by diluting a known volume and concentration of an inert gas (usually helium) in the lungs by breathing the gas mixture (contains helium, N_2 and O_2) in a closed system. The patient begins

A4. Measurement of Hyperinflation during Rest and Exercise

the test by breathing room air for approximately 1 minute while wearing nose clips. This period of resting breathing familiarizes the patient with the breathing apparatus and ensures stability of FRC. The patient is then switched to breathing the helium gas mixture at FRC and the patient continues to breathe until the helium equilibrates in the lungs. Equilibration occurs when the helium concentration is <0.02% for 30 seconds. The test typically takes less than 10 minutes to complete in most patients. Inert gas dilution is calculated as follows:

$$FRC_{He} = V_{app} (C_1 - C_2) / C_2$$

where Vapp is the volume of the breathing apparatus, C_1 is the initial concentration of helium, and C_2 is the concentration of helium after equilibration.

The inert gas dilution method is a widely used, simple, reproducible, and relatively inexpensive method for determining FRC. However, this method only measures the gas volume in the lungs in communication with the mouth; like the N_2 washout technique, the inert gas dilution method does not measure trapped gas which will ultimately underestimate FRC in patients with obstructive lung diseases. Thus, diagnosis of LH based on FRC_{He} must also be made with caution.

Measurement of RV and TLC

There are two recommended methods for determining TLC and RV from FRC. The preferred approach is to measure ERV and slow inspiratory vital capacity (IVC) immediately after measuring FRC. The patient should remain on the mouthpiece for all maneuvers since they are performed in a "linked" fashion. Values for RV and TLC are determined as follows:

$$RV = FRCmean - ERVmean$$
$$TLC = RV + IVClargest$$

The alternative approach involves the measurement of IC immediately following the measurement of FRC. The VC can be performed separately using either a slow IVC or slow expiratory VC. The patient is allowed to come off the mouthpiece between linked FRC and IC measurements and between separate VC maneuvers. This approach may be required for the severely dyspneic patient that is not capable of performing the FRC measurement with a linked ERV maneuver. Values for RV and TLC are determined as follows:

$$RV = TLCmean - VClargest$$
$$TLC = FRCmean + IC$$

Measuring Hyperinflation during Exercise

Dynamic LH during exercise refers to the increase in EELV relative to resting values. The physiological, sensory, and clinical consequences of Hyperinflation have been described in detail in other chapters of this book. EELV can be measured during exercise using gas dilution techniques, optoelectronic plethysmography or respiratory inductance plethysmography. However, these techniques can be technically challenging and are not routinely used for clinical diagnostic purposes. The most common and widely accepted method of measuring EELV during exercise is to have patients perform serial IC maneuvers throughout a cardiopulmonary exercise test. An example of an IC maneuver is shown in **Figure 2**. This is a relatively simple measurement to perform and most commercially available metabolic systems have the required software to obtain ICs during exercise. Despite the simplicity of this measurement relative to other methods, there are several important factors

A4.
Measurement of Hyperinflation during Rest and Exercise

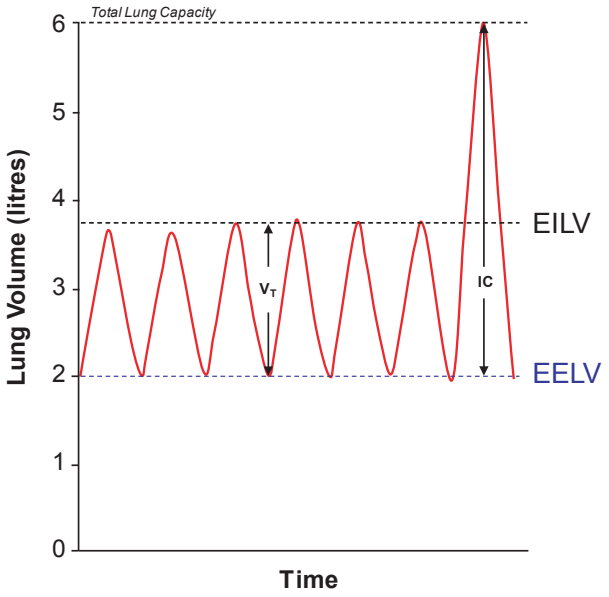

Figure 2. *Example of a correctly performed inspiratory capacity maneuver. The blue dashed line represents the correct way of anchoring the IC to the appropriate EELV.EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume; V_T: tidal volume; IC: inspiratory capacity.*

and assumptions that must be considered in order to accurately measure EELV during exercise. This chapter will describe the important methodological considerations of this technique and will describe the wealth of data that can be obtained from IC maneuvers.

Assumptions

The EELV during exercise is calculated as the difference between TLC and IC. The accuracy of this approach critically depends on TLC remaining constant throughout exercise. If one assumes TLC does not change as supported by previous studies in health and chronic obstructive pulmonary disease (COPD), then it is reasonable to conclude that changes in IC reflect changes in EELV. Equally important is that subjects reach TLC when performing the IC maneuver. This can be difficult to verify, but standardized instructions and verbal encouragement as described later can mitigate concerns surrounding the attainment of TLC during the maneuver.

The ability to accurately track changes in EELV during exercise using the IC maneuver clearly depends on the reproducibility of this method. Indeed, several studies confirm that IC maneuvers are reproducible, at least in patients with COPD during cycle exercise. Even in the setting of large multicenter clinical trials, the IC appears to be highly reproducible at rest and throughout exercise. However, limited data exists on the reproducibility of the IC in different clinical populations and using different exercise modalities (*e.g.,* treadmill).

Performing IC maneuvers

The presence of dynamic Hyperinflation (DH) is based on the changes in EELV (or IC) relative to resting values. Thus, the first step is to establish a reproducible baseline measurement of IC. During baseline IC maneuvers, the patient should assume the same position that they will use during the cardiopulmonary exercise test. Patients should perform at least 3 minutes of resting tidal breathing to become accustomed to the breathing apparatus and to minimize their anxiety due to the anticipation of exercise. Generally, patients should perform a minimum of 3 acceptable IC maneuvers during the resting

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Measurement of Hyperinflation during Rest and Exercise

period. Limited data is available on the criteria for reproducibility of ICs, but it is suggested for measurements to agree within 5% or 60 millilitres of the mean, whichever is greater. Although this is a stringent cut-off, it provides some general guidelines on reproducibility. The mean of the two most reproducible IC measurements can be used as the baseline value. Once the resting period is completed, an IC maneuver should be performed near the end of each exercise stage. If using an incremental exercise test, it is recommended to use stepwise increases in work rate rather than ramp increases. The step increases in work rate (*e.g.,* 20W every 2 minutes) will allow for more stable ventilations compared to a ramp protocol where subtle incremental increases in work rate and ventilation can influence the anchoring of IC measurements to the appropriate EELV.

Detailed instructions before and during the maneuver have been described previously. Briefly, the subject should be encouraged to perform a maximal inspiration from a stable EELV to TLC. The technician should provide a prompt for the maneuver (*e.g.,* "at the end of a normal breath out, take a deep breath all the way in, until you are completely full"). The maneuver should be performed quickly and forcefully to ensure that the subject is fully inflated. Providing a demonstration to the patient can also be very helpful. Enthusiastic verbal encouragement during the IC maneuver is strongly recommended (*e.g.,* "in, in, in,"). Some subjects have a difficult time initiating the IC maneuver at a stable EELV or they have marked alterations in their breathing pattern for several breaths prior to the maneuver. This can usually be identified during the rest period or early during exercise. The technician should attempt to re-explain the maneuver if the patient continues to have difficulties. Patients who have significant alterations in their breathing pattern for several breaths after the prompt is given should be encouraged to perform the maneuver as soon as possible. In some cases, the instructions may need to be modified if patients are taking too long to perform the maneuver (*e.g.,* "at the end of the next breath out, take a deep breath all the way in until you are completely full").

Data Analysis

It is important to emphasize that the accuracy of the IC is dependent on measuring both inspiratory and expiratory volumes continuously throughout the test. This allows the technician to anchor the IC to the appropriate EELV (**Figure 2**). If inspiratory volume alone is measured, it can lead to incorrect values for the IC, because it will not allow the investigator to account for the EELV preceding the maneuver. For example, subjects may prematurely initiate the IC maneuver before reaching the appropriate EELV. If the technician only measures the volume of the IC breath without accounting for the EELV of the previous breaths, then they will significantly underestimate the IC. Similarly, if the subject expires beyond the baseline EELV, then the IC would be overestimated. The blue dashed lines in **Figure 2** demonstrate the correct way of anchoring the IC to the appropriate EELV. Some commercially available systems allow the user to drag a horizontal line to the appropriate EELV. It is important for the breaths used to determine EELV to be corrected for signal drift. Some degree of drift occurs in all flow sensing devices and most commercially available systems account for this.

A4. Measurement of Hyperinflation during Rest and Exercise

Interpretation

The absolute increase in EELV (or decrease in IC) that classifies a patient as a dynamic hyperinflator has not been firmly established. There is also no grading system available to classify the severity of DH. Some have defined DH as a decrease in IC from rest > 150ml or 4.5% predicted during exercise. This is based on the work of O'Donnell *et al.* who found that that the 95% confidence interval for the resting IC measurement was ± 0.14 litres or ± 4.5% predicted, indicating that reproducibility criteria of within 150ml is appropriate for testing IC; at least in COPD patients. The 95% CI for peak exercise IC was similar. Others have defined DH as a decrease by more than 1.96 standard deviations below the baseline IC measurements, a decrease in IC by 10% from baseline or 10% below predicted, or as a slope higher than zero from the linear regression of EELV as a function of time. Clearly there is no accepted operational definition of DH and future research is needed before definitive recommendations can be made.

The regulation of EELV appears to be highly variable in patients with COPD. For example, different patterns of DH have been identified such as "early hyperinflators" and "late hyperinflators". It is also becoming increasingly recognized that a subset of COPD patients (~15%) do not dynamically hyperinflate during exercise. Non-hyperinflators have been termed "euvolumics". **Figure 3** shows three individual patients with COPD with differing patterns of EELV regulation during constant load cycle exercise. Patient A immediately increases EELV during exercise ("early hyperinflator") and at peak exercise the EELV was 1.09l above resting values. In contrast, patient B does not increase EELV until later during exercise ("late hyperinflator"). The magnitude of DH is significantly smaller in patient B compared to patient A (blue shaded region). At peak exercise, EELV was 0.34l above resting values in patient B. Finally, patient C does not increase EELV during exercise (*i.e.,* non-hyperinflator). This patient's EELV actually decreases relative to resting values throughout exercise.

Additional Information Gained from Inspiratory Capacity Maneuvers

Operating lung volume plots as shown in **Figure 3** also provide visualization and quantification of important lung volumes such as the end-inspiratory lung volume (EILV) and IRV. Simply assessing the change in EELV relative to rest without considering these other lung volumes can be misleading when diagnosing ventilatory limitations during exercise. For example, patient A demonstrates a substantial amount of DH during exercise compared to patient B and C (**Figure 3**). However, patient B and C have much higher EILV values relative to TLC and thus a smaller IRV. Some suggest that perhaps the EILV is as important, if not more important, than EELV during exercise. Patient C does not dynamically hyperinflate during exercise, but still has constraints on tidal volume expansion and breathes close to TLC where the elastic work of breathing is high. Patients that do not dynamically hyperinflate but still breathe close to TLC often have a smaller resting IC and high levels of static Hyperinflation. Thus, it is important that ventilatory limitations be assessed by examining all operating lung volumes during exercise in conjunction with resting measures of LH.

A4.
Measurement of Hyperinflation during Rest and Exercise

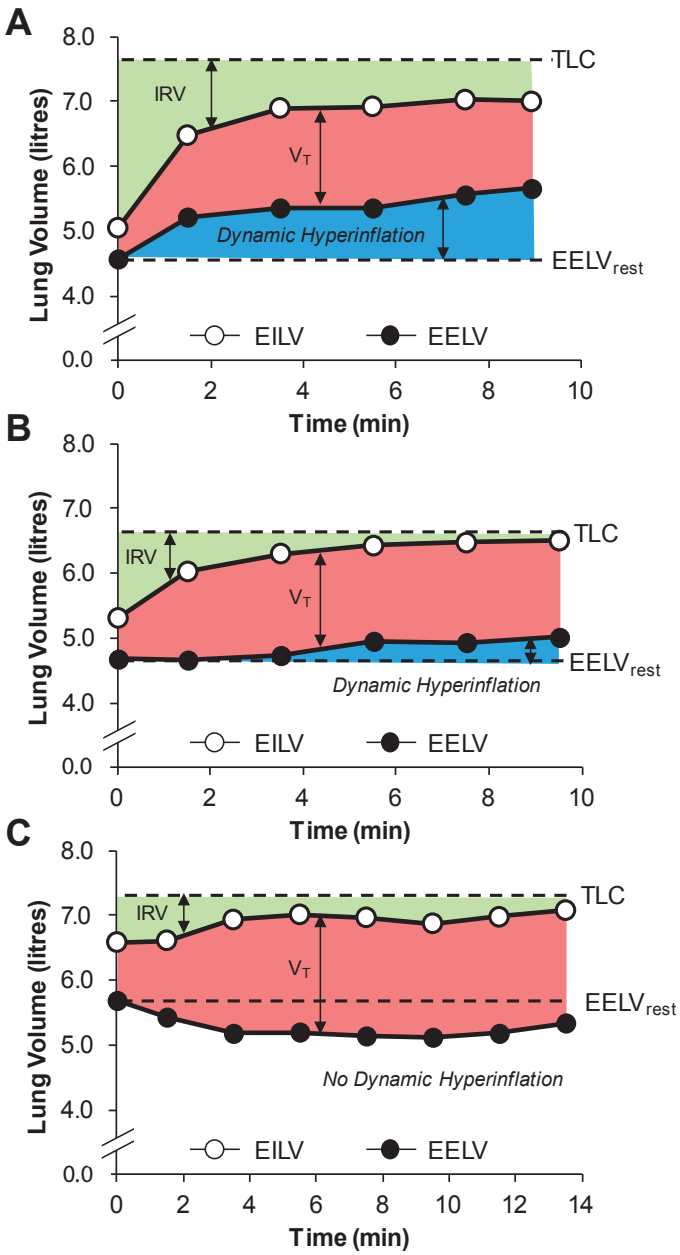

Figure 3. *Examples of different operating lung volume plots in three patients with chronic obstructive pulmonary disease. The green region represents the IRV, the red region represents V_T and the blue region represents the increase in EELV relative to resting values (i.e.,: DH). TLC: total lung capacity; IRV: inspiratory reserve volume; V_T: tidal volume; EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume; $EELV_{rest}$: resting end-expiratory lung volume.*

A4.
Measurement of Hyperinflation during Rest and Exercise

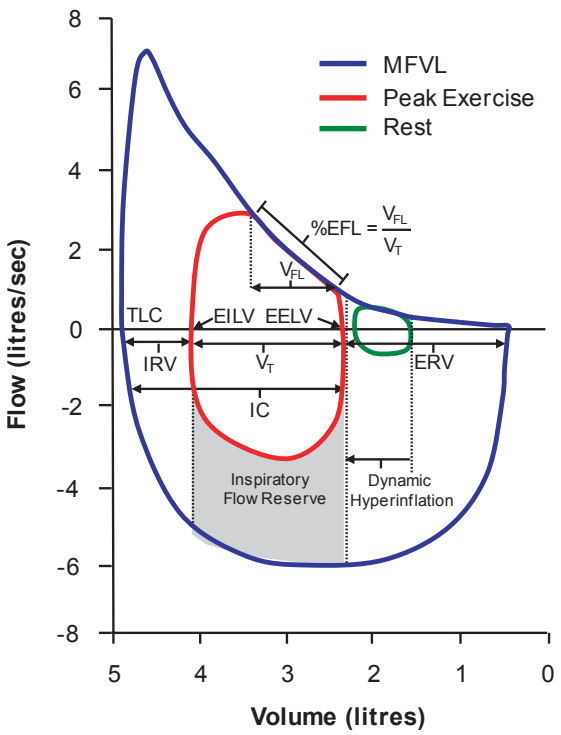

Figure 4. *Example of tidal flow volume loops at rest (green line) and peak exercise (red line) superimposed within a MFVL (blue line) in a patient with mild chronic obstructive pulmonary disease. The magnitude of expiratory flow limitation can be calculated as the volume that overlaps the MFVL divided by the V_T. Dynamic hyperinflation is characterized by a leftward shift (i.e.: increase) in end-expiratory lung volume compared to rest. MFVL: maximum flow volume loop; EFL: expiratory flow limitation; V_{FL} : volume of tidal breath that is flow limited; V_T: tidal volume; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; IC: inspiratory capacity; TLC: total lung capacity; IRV: inspiratory reserve volume; ERV: expiratory reserve volume. Modified and reproduced with permission from Guenette et al. (Pulm Med: 2013).*

The IC maneuver not only allows the clinician to measure DH during exercise, but it also provides considerable insight into other indices of ventilatory limitation. For example, **Figure 4** shows resting and peak exercise tidal flow-volume loops plotted within a maximal flow-volume loop in a patient with mild COPD. The IC maneuver permits the determination of EELV which allows for the correct placement of the tidal breaths along the volume axis of the maximal flow-volume loop. These plots allow the clinician to easily view factors other than just DH during exercise (*e.g.,* inspiratory and expiratory flow reserves, expiratory flow limitation, IRV, etc.). Most commercially available metabolic systems allow users to construct flow-volume loop plots. However, caution must be exercised when interpreting expiratory flow limitation using these plots if thoracic gas compression and exercise induced bronchodilation are not accounted for in the maximum flow-volume loop.

CONCLUSION

Lung Hyperinflation at rest and during exercise is associated with a number of adverse clinical consequences as outlined in this book. The correct diagnosis of both static and dynamic Hyperinflation is clearly dependent on the validity, reliability, and underlying assumptions of the various methods used to measure lung volumes. Resting Hyperinflation depends on the accurate measurement of FRC, which is used to calculate RV and TLC. Increases in these parameters >120-130% predicted is usually indicative of resting LH. Plethysmography, N_2 washout, and multiple breath inert gas dilution are three commonly used methods to measure FRC. In contrast to plethysmography, N_2 washout and the inert gas dilution methods do not measure trapped gas in patients with

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Measurement of Hyperinflation during Rest and Exercise

obstructive lung diseases. Thus, FRC values will be underestimated using these methods compared to the gold standard method of plethysmography. The most commonly used method of assessing Hyperinflation during exercise is to have subjects perform serial IC maneuvers in order to track changes in EELV relative to resting values. In addition to measuring dynamic Hyperinflation, IC maneuvers can be used to examine other important lung volumes during exercise such as EILV and IRV. Additional valuable insight can be gained when combining this information with detailed flow-volume loop analysis.

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B.

CLINICAL

B1.
Clinical Consequences of Lung Hyperinflation

B2.
Lung Hyperinflation in Respiratory Childhood Diseases

B1.
Clinical Consequences of Lung Hyperinflation

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CLINICAL

B1.
Clinical Consequences of Lung Hyperinflation

Key Points

1.
Clinical signs of lung hyperinflation are high position of the shoulders and pursed lip breathing.

2.
Tympanic and diminished breath sound, abnormal movements of the thoracic wall, Hoover's sign and pulsus paradoxus may also be found during clinical examination.

3.
Dyspnea is the cardinal symptom of lung hyperinflation, primarily during exertion-limiting exercise.

4.
Dyspnea due to lung hyperinflation leads to reduced physical activity, deconditioning, anxiety and depression; thus significantly affecting quality of life.

5.
Lung hyperinflation has detrimental effects on the cardiovascular system.

6.
Lung hyperinflation is related to increased mortality and morbidity.

B1.
Clinical Consequences of Lung Hyperinflation

INTRODUCTION

In previous chapters, the importance of lung hyperinflation (LH) in the mechanics of breathing was analyzed. It is shown that LH increases the work of breathing, and in turn causes fatigue of the respiratory muscles and respiratory failure. Lung hyperinflation may be observed at rest (static hyperinflation developed over the years), but it may be exaggerated transiently during hyperventilatory conditions, *i.e.*, exercise and exacerbation, that we define as dynamic hyperinflation (DH).

In this chapter we are going to discuss the clinical signs and symptoms that are attributed to LH, the effect of LH on quality of life, the effects of LH on morbidity and mortality and the clinical effects of LH on the cardiovascular system.

Clinical Signs of LH

Clinical examination can reveal the following signs of LH:

- High position of the shoulders and barrel chest (consequences of LH on the rib cage);
- Pursed lip breathing, which is a compensatory mechanism to fight the intrinsic positive end-expiratory pressure (PEEP) produced by LH;
- Forward leading posture due to severe LH;
- Tympanic sounds and diminished motion of the diaphragm on percussion and diminished breath sounds on auscultation;
- Abnormal movements of the chest wall, such as asynchronous motions (time lag between the motion of the ribcage and abdominal compartments), paradoxical motion (one compartment moving in the opposite direction of the other), respiratory alternates (increase in the breath-to-breath variability of the relative contribution of the rib cage and abdomen). All the above signs could indicate respiratory muscle fatigue;

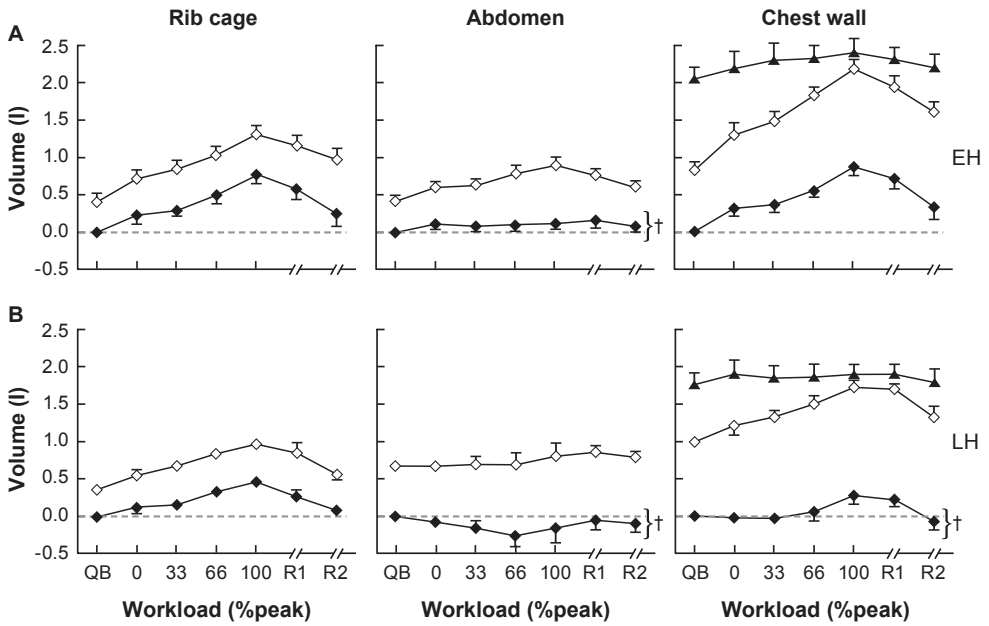

Figure 1. Volumes of the rib cage and abdominal compartments and of total chest wall in (A) early hyperinflators (EH) and (B) late hyperinflators (LH) expressed in absolute values during quiet breathing (QB), exercise, and recovery (R1 and R2). Open circles indicate end of inspiration; closed circles indicate end of expiration; triangles indicate chest wall volumes at total lung capacity. †Significant differences in time points between groups.

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Clinical Consequences of Lung Hyperinflation

- Hoover's sign, showing distortions of the ventilator pump (see chapter B2);
- Pulsus paradoxus, which is a sign of the drop of systolic blood pressure of more than 10 mm of Mercury when measured at high lung volumes (LH in asthma).

Clinical Symptoms of LH (Dyspnea)

The major clinical symptom related to LH is dyspnea. In chapters A2-A3, the relationship of LH and the symptom of dyspnea was discussed in detail from the pathophysiological point of view. This cardinal symptom is more prominent during exertion and has as a consequence exercise intolerance and limitation.

Hyperinflation and Exertional Dyspnea/Exercise Intolerance

Exertional dyspnea is one of the main factors limiting physical activity in patients with chronic obstructive pulmonary disease (COPD). The mechanism for the ventilatory limitation of exercise in COPD patients is related to expiratory flow limitation and dynamic hyperinflation (DH). Initially, DH acts as a compensatory mechanism in an attempt to increase expiratory flows to accomplish the increase in tidal volume needed for hyperventilation during exercise. Dynamic hyperinflation is a better exercise strategy in COPD than expiratory muscle recruitment, but the benefit it confers is small.

It is interesting to mention that not all COPD patients who adopt the strategy to hyperinflate during exercise follow the same time course of DH during exercise. In a study with measurements of operational lung volumes via optoelectronic plethysmography, it was shown that there are two distinct patterns of change in the chest wall volume response to exercise in patients with severe COPD (**Figure 1**); namely early hyperinflators and late hyperinflators. These two groups did not differ in terms of resting lung volumes or exercise tolerance measures. In the early hyperinflator patients, the end-expiratory lung volume (EELV) increases from the beginning of exercise and keeps increasing progressively throughout exercise; while in the late hyperinflator group, the EELV remains unchanged up to 66% peak work rate (Wpeak), but increases significantly at Wpeak. Although at the limit of tolerance the increase in EELV was significantly greater in the early hyperinflator group than in the late hyperinflator group, both reached similar values of Wpeak, inspiratory reserve volume (IRV) and dyspnea. Furthermore, the sensations of dyspnea and leg discomfort tended to be higher in the early hyperinflator group than in the late hyperinflator group (**Figure 2**). However, the differences between the groups were not significant.

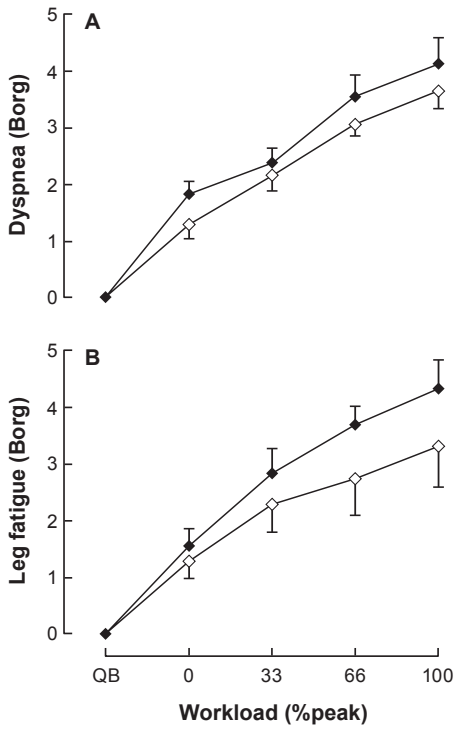

Figure 2. *Perceptions of (A) dyspnea and (B) leg discomfort at quiet breathing (QB) and during exercise between early (closed symbols) and late hyperinflators (open symbols).*

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Clinical Consequences of Lung Hyperinflation

Although DH during exercise is a compensatory mechanism that increases expiratory flow, it has several disadvantages including

- Dynamic hyperinflation, as mentioned above, shifts the tidal breathing range closer to total lung capacity (TLC) with a consequent decrease in IRV, and reduces the ability of tidal volume to expand appropriately during exercise;
- In some COPD patients, this mechanical constraint on tidal volume expansion may lead to hypercapnia and arterial oxygen desaturation during exercise;
- By producing a positive end-expiratory alveolar pressure (intrinsic PEEP) that must be overcome to initiate the next breath, the load is increased on the inspiratory muscles; thus increasing the work and oxygen cost of breathing;
- Dynamic hyperinflation results in an operational inspiratory muscle weakness with reduction in maximal inspiratory pressure (MIP) measured at the mouth (**Figure 3**) by shortening the muscle fibers in the diaphragm and consequently placing the inspiratory muscles at a mechanical disadvantage due to length-tension effects (**Figure 4**);

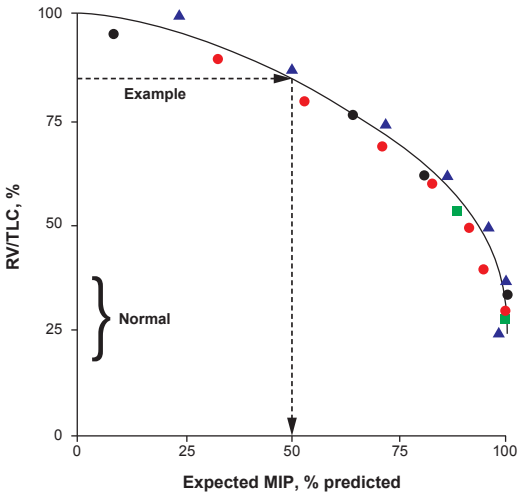

Figure 3. *The MIP is 100 percent of its predicted value when the RV/TLC is in its normal range (20 to 35 percent depending on age). Maximal inspiratory pressure decreases as RV/TLC increases, because diaphragm muscles begin to operate at a mechanical disadvantage. As an example (dashed lines), a 55-year-old man with severe COPD and severe hyperinflation (RV/TLC of 85 percent) has a MIP that is only 50 percent of its predicted value (50 cmH_2O instead of 100 cmH_2O), despite having good nutrition and normal inspiratory muscle strength.*
MIP: maximal inspiratory pressure; TLC: total lung capacity; RV: residual volume.
Adapted from: Rochester DF. Tests of respiratory muscle function. Clinics Chest Med 1988; 9:249-261.

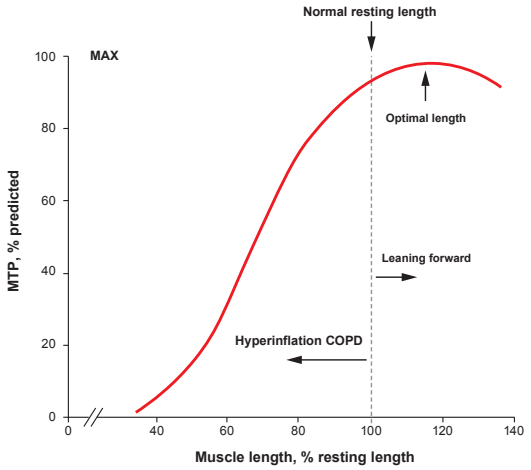

Figure 4. *Hyperinflation (decreased muscle length) causes reduced maximal inspiratory pressure (MIP) in many patients with COPD. The MIP is 100 percent of its predicted value when the muscle length is in its normal range. MIP decreases as muscle length decreases.*

- Dynamic hyperinflation adversely affects the dynamic cardiac function;

All of the above negative effects of DH are clearly interdependent and contribute, in a complex, integrated manner to the development of exertional dyspnea. Exertional dyspnea in COPD, which is related mostly to DH during exercise, among other factors, leads to exercise intolerance.
However, it should be noted that dyspnea with

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Clinical Consequences of Lung Hyperinflation

exertion and impaired exercise capacity are nonspecific complaints in patients with COPD and are not attributed only to DH. Additional causes of dyspnea with exertion may include:

- Blood gas abnormalities;
- Respiratory muscle weakness;
- Peripheral skeletal muscle weakness/ atrophy;
- Impaired cardiac performance during exercise;
- Increased ventilatory demand due to physiologic dead space, hypoxemia, hypercapnia, early onset lactic acidosis, deconditioning, and/or poor nutrition;
- Increased symptom perception; and
- Psychological disorders (anxiety, depression).

Thus, a patient with COPD who complains about dyspnea with exertion cannot be assumed to have only DH: additional diagnostic testing is required.

Finally, due to dyspnea on exertion, COPD patients progressively reduce motions. This has other deteriorating effects, such as skeletal muscle deconditioning, anxiety and depression. This is the so-called "vicious circle of dyspnea on exertion" (**Figure 5**). As a result of the above, the QoL of those patients is tremendously decreased.

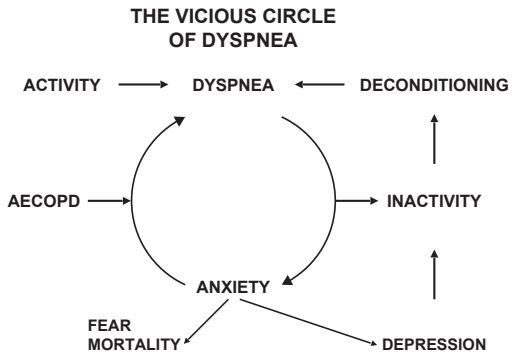

Figure 5. *The vicious circle of dyspnea: activity. Produce dyspnea that make the patient deconditioned due to anxiety. Deconditioning makes the patient more dyspnoic. In addition acute exacerbations (AECOPD)induce more dyspnea and enhance the fear of death, thus drammaticaly affect the QoL.*

Hyperinflation and Cardiovascular Performance

There is growing recognition that COPD and its frequent cardiovascular comorbidities, such as arterial hypertension, coronary artery disease or congestive heart failure, are related not only to the common risk factor of cigarette smoking and ageing, but appear to be linked by an underlying systemic inflammatory status as well. The inflammation associated with COPD is not limited to the lung, but can also affect non-pulmonary organs such as the cardiovascular system.

At the same time, lung mechanics and cardiac performance are deeply dependent on each other. Both may be responsible for exercise limitation, exertional dyspnea, and poor QoL in the presence of irreversible airflow limitation and LH. Furthermore, muscle mass depletion, especially in patients with pulmonary emphysema among the COPD population, may also contribute to cardiovascular response to exercise. Interestingly, in pulmonary emphysema, changes both in lung mechanics and in skeletal muscle pump may impair the cardiovascular function per se.

Hyperinflation and the Left Heart

Apart from the well-known effect of dilated right ventricle (due to the development of chronic pulmonary hypertension in COPD) in the leftward displacement of the interventricular septum and the consequent decrease in size of the left ventricle, pulmonary hyperinflation per se can significantly affect heart size and its function. The recently published Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study documented that pulmonary hyperinflation is associated with greater left ventricular mass.

By means of magnetic resonance technique,

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Clinical Consequences of Lung Hyperinflation

Jörgensen *et al.* studied patients with severe emphysema and found a decrease in intrathoracic blood volume in the left ventricular and right ventricular end-diastolic volumes and an impaired stroke volume and stroke work in hyperinflated lungs, as compared to controls. The authors argued that there are at least two main explanations of these findings: in the presence of hyperinflated lungs, a high PEEPi could cause intrathoracic hypovolemia and small end-diastolic dimensions of both the left and right ventricular chambers. The redistribution of pulmonary circulation in emphysema might occur, not only because of a direct parenchymal destruction or hypoxia vasoconstriction, but also because of decreased compliance of the pulmonary vascular bed. Secondly, the right and left ventricular chambers could be mechanically compressed by hyperinflated lungs that could worsen end-diastolic stiffness. According to the Frank-Starling law, a low preload finally reduces ventricular performance in terms of stroke volume and stroke work.

In a large sample of COPD patients ranging from GOLD stage 1 to 4, Watz *et al.* found that the degree of COPD severity was directly correlated to heart dysfunction. Interestingly, in this study, the cardiac chamber sizes and impaired left ventricular diastolic filling pattern correlated more to the degree of static hyperinflation, as assessed by inspiratory capacity-to-total lung capacity ratio (IC/TLC), than to the degree of airway obstruction, expressed as forced expiratory volume in 1 second (FEV_1) % pred., or to diffusion capacity to carbon monoxide. Furthermore, IC/TLC was an independent predictor of cardiac chamber sizes after adjustment for body surface area.

In line with the findings by Watz *et al.*, Malerba *et al.* reported a frequent subclinical left ventricular filling impairment in COPD patients at the earlier stage of the disease, even in the absence of any other cardiovascular disorder. Furthermore, Smith *et al.* have recently shown a reduction of pulmonary vein dimension in COPD which is related to emphysema; thereby supporting a mechanism of upstream pulmonary causes for left ventricle underfilling. Interestingly, pulmonary hyperinflation may have negative effects, but pulmonary deflation has the potential to improve the cardiac function in patients with pulmonary emphysema. In severely hyperinflated patients, Come *et al.* recently found that decreased hyperinflation through lung volume reduction surgery is significantly associated with an improvement in oxygen pulse, which may be considered as a noninvasive marker of cardiovascular efficiency and a measure of stroke volume.

It is of note that the extent of emphysema as detected by computed tomography (CT) may be associated with impaired cardiac function, even in patients without very severe lung disease. In a recent population-based study, a greater extent of emphysema on CT scanning was linearly related to impaired left ventricular filling, reduced stroke volume and lower cardiac output, without changes in the ejection fraction; whereas smoking status significantly worsened these associations. Accordingly, the authors hypothesized that due to the mechanisms of the impaired left ventricular filling in too early, mild emphysema might be the subclinical loss of capillary bed due to the apoptotic effect of smoking on the pulmonary endothelium.

Cardiovascular Response to Exercise and Dynamic Hyperinflation

As mentioned above, DH is responsible for limitation of exercise in COPD patients and for the onset of exertional dyspnea. Accordingly, it is conceivable that, during exercise, DH can

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Clinical Consequences of Lung Hyperinflation

further worsen a poor resting cardiac function in patients with COPD.

Both ventilatory and cardiac responses to exercise can be studied sufficiently with a cardiopulmonary exercise test (CPET). The cardiopulmonary exercise tests is a relatively noninvasive method to test tolerance to maximal exercise, and gives several pieces of information about how cardiovascular, respiratory and muscle apparatuses respond to exercise. Notably, the assessment of DH is based on the comparison of the IC performed at rest and during exercise. A positive difference between them is an indication of DH; assuming that TLC remains constant during exercise.

Dynamic hyperinflation, which impairs the cardiovascular function in COPD patients, may be documented during rapidly incremental CPET. Vassaux *et al.* first observed that DH is negatively associated with oxygen pulse at peak of exercise in patients with severe COPD. These results were confirmed and extended in COPD patients with different degrees of severity, by showing a significant relationship between DH and a battery of noninvasive measures of cardiovascular function during exercise.

Importantly, it has been recently shown that in patients with severe pulmonary emphysema, the reduction in DH after lung volume reduction surgery was significantly associated with an improvement in cardiac response to exercise; both in terms of oxygen pulse and pulse pressure, which is the difference between systolic and diastolic blood pressure. It is of note that pulmonary rehabilitation may lower the ventilatory demand during exercise, resulting in the prolongation of expiration time, and, subsequently, in the reduction of DH. Accordingly, one may hypothesize that, in COPD patients, pulmonary rehabilitation may improve the cardiovascular response to exercise by enhancing the ventilatory function.

Mortality and LH

A number of important studies have shown a relationship between mortality rates or survival and LH. **Figure 6** illustrates the results of one of those studies; showing that if IC<80% pred. then the overall cause as well as respiratory cause mortality of these patients is significantly increased. In addition, there is a strong relationship between the degree of hyperinflation and hospital admissions due to COPD. It is obvious that LH affects QoL, morbidity and mortality of those patients significantly.

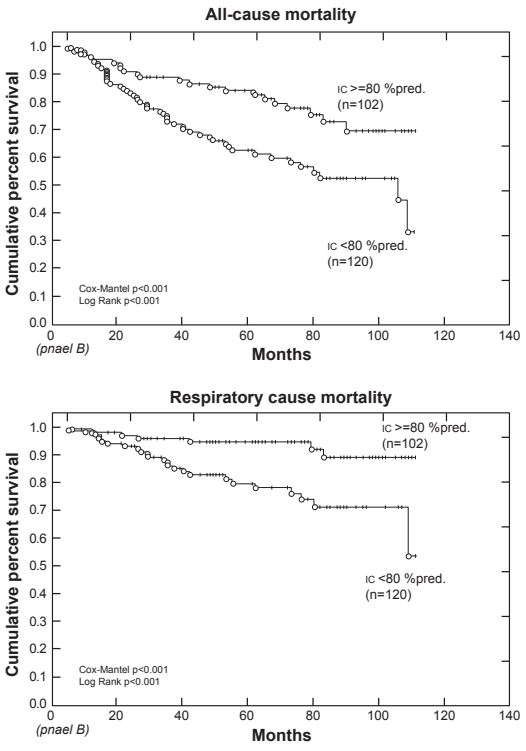

Figure 6. *Hyperinflation evaluated by IC, affecting respiratory bul also all-cause mortality. (TANLUCCI et al)*

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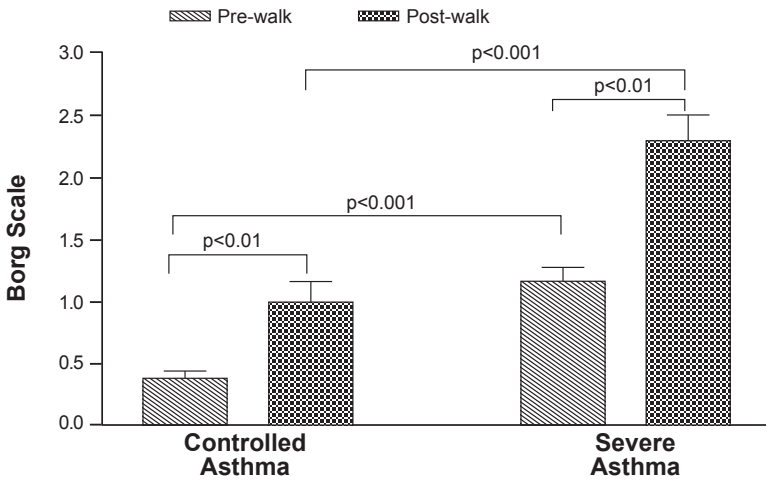

Figure 7. The effect of 6 min waking test on dyspnea measured by Borg scale in well controled and severe asthmatics (unpuplised data).

Lung hyperinflation in Asthma

A multi-national European study (European Network For Understanding Mechanisms Of Severe Asthma [ENFUMOSA]) has shown that patients suffering from severe asthma had an increased RV/TLC ratio compared to those with controlled asthma. This signifies that severe asthmatics, even at a steady stage condition, had a degree of LH. That was also postulated by the decrease seen in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). It is obvious that this static hyperinflation increases significantly during exercise or an acute dynamic attack. **Figure 7** shows the effect of a 6min walking test on dyspnea index in controlled and severe asthmatics. As discussed in other chapters DH is a rather compensatory mechanism to counterbalance airway obstruction and airflow limitation; but the increase in work of breathing and respiratory muscle insufficiency could lead to respiratory failure or even death. This is seen in the severe attack of status asthmaticus.

CONCLUSIONS

Lung hyperinflation is a frequent pathophysiological condition of the chronic airway diseases. It affects the QoL of patients significantly and has been associated with high morbidity and mortality.

Therefore, physicians taking care of these patients must have adequate knowledge of this condition and of the modes of treatment that could reverse LH.

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Clinical Consequences of Lung Hyperinflation

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B2.
Lung Hyperinflation in Respiratory Childhood Diseases

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CLINICAL

B2.
Lung Hyperinflation in Respiratory Childhood Diseases

Key Points

1.
A number of essential differences in airway resistance, lung volume, efficiency and endurance of respiratory muscles between adults and children should be taken into account for the correct assessment and interpretation of hyperinflation in children.

2.
Hyperinflation is present in a high proportion of asthmatic children, is correlated with the disease severity and responds to treatment with bronchodilators and inhaled corticosteroids.

3.
Children with acute bronchiolitis commonly show hyperinflation that correlates with the degree of obstruction, which in turn remits with age in the majority. In bronchiolitis obliterans, the hyperinflation tents to persist for many years.

4.
Hyperinflation is detected early in the course of cystic fibrosis and is correlated with disease severity, genotypes, microbial colonization and exercise ability.

5.
Classic spirometry parameters are poor markers of the small airway disease leading to hyperinflation. Lung volumes or air trapping quantification by high-resolution computed tomography should be included in the evaluation of chronic respiratory diseases in childhood.

CLINICAL

B2.
Lung Hyperinflation in Respiratory Childhood Diseases

INTRODUCTION

In clinical practice, hyperinflation is a common feature (otherwise known as air trapping) in obstructive pulmonary diseases such as chronic obstructive pulmonary disease (COPD), asthma, bronchiolitis, bronchiectasis, and cystic fibrosis (CF).

Although pediatric patients are commonly presented with airway obstructive diseases such as asthma, bronchiolitis or CF, hyperinflation is not extensively studied in these patients.

As shown in previous chapters of this book, hyperinflation and its consequences on the human lung depend on various factors, such as airway resistance, lung volume, efficiency and the endurance of respiratory muscles. There are a number of essential differences in lung mechanics between adults and children that should be taken into consideration for the correct assessment of any ill child and the interpretation of any pulmonary function performed in young children.

Clinically, the most important difference is that the basal metabolic rate is higher in infants than in adults. Moreover, oxygen consumption is three times higher compared to that of adults (7 ml/kg/min in children, compared to 3 ml/kg/min in adults). Additionally, it should be mentioned that infants present high respiratory and cardiovascular activity at rest accompanied with lower functional residual capacity (FRC) compared to that of adults. These factors reduce the respiratory reserve and facilitate dyspnea and fatigue of the respiratory muscles during stressful events.

It is well known that the lungs and airways do not grow isotropically, since the bronchial system is fully developed at the sixth month of gestation before the alveolar development begins. Most alveoli are developed after birth until the third year of life through multiplication; this means that infants and young children have increased lower airway resistance and decreased elastic recoil. Moreover, since the airways of children are comparatively smaller, even minor changes in airway radius (*i.e.,* asthma, bronchiolitis) can cause a major increase in airflow resistance which increases by the fourth power of any reduction in radius.

Contrary to the adult lung where periphery contributes less than 20% to the total airway resistance, the contribution of the small peripheral airways in infants is 50%. This is the reason of the significantly severe problems caused by diseases such as bronchiolitis, which mostly affects lung periphery. Despite lower airway resistance, upper airway resistance is increased as well, due to nasal breathing, larger tongue and increased compliance of infant's larynx, trachea and bronchi.

The chest wall of infants has horizontally placed, high compliant ribs and poorly developed intercostal muscles. During inspiration, contraction of the diaphragm (which is more horizontal than that of adults) will move the rib inward. In case of hyperinflation, the diaphragm is flat and spends energy to overcome this by constriction of the costal margin during inspiration. This inward motion of the costal margin, paradoxically present during inspiration, is called Hoover's sign, and is a common symptom of peripheral obstruction and hyperinflation in infants (**Figure 1**).The same paradoxical inward motion has been recorded in patients with COPD and hyperinflation.

The basic features of hyperinflation in most common pediatric diseases such as asthma, bronchiolitis, CF and in some rare diseases will be discussed in the following pages.

B2.
Lung Hyperinflation in Respiratory Childhood Diseases

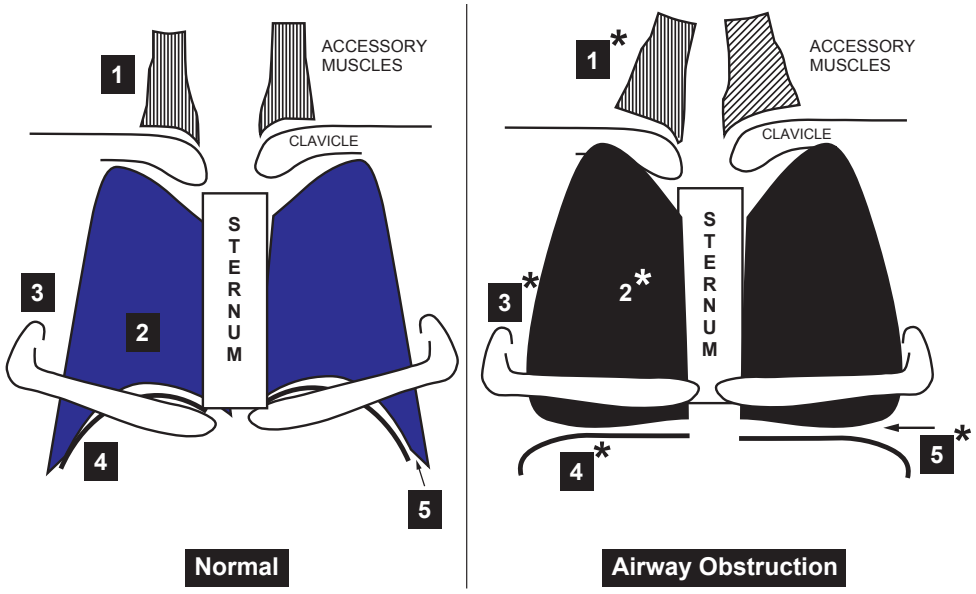

Figure 1. *Mechanism behind Hoover's sign. 1*) Accessory muscles; 2*) hyper-expansion of the lungs; 3*) alteration of rib orientation to horizontal; 4*) flattened diaphragm and 5*) decreased zone of apposition.*
Adapted from Mason: Murray and Nadel's Textbook of Respiratory Medicine, 4th Edition.

Asthma

Asthma is the most common chronic childhood disease that presents hyperinflation which could be documented either by increases of the residual volume (RV), of the ratio of residual volume to total lung capacity (RV/TLC) or of the functional residual capacity (FRC), or by chest high-resolution CT (HRCT) or magnetic resonance imaging (MRI) scans.

The degree of hyperinflation in asthma usually correlates with the severity of bronchospasm. In conditions of bronchoconstriction, the hyperinflation is mostly determined by dynamic factors. The major contributing factor to dynamic hyperinflation is increased airway resistance with prolonged expiratory time constants, resulting in slower and incomplete lung emptying (air trapping). Physiologically, this is expressed as elevation at end expiratory lung volume (EELV) above the relaxation volume of the lung (Vr). Hyperinflation is often present in some degree at rest and increases further on exercise or exacerbations where the obstruction is augmented (dynamic hyperinflation). In healthy individuals during exercise, the increased respiratory demands cause an elevation of the respiratory rate and tidal volume (V_T) expansion. This increased expiratory effort progressively decreases EELV in order to allow complete exhalation of the expanded inhaled V_T before the next inhalation (**Figure 2**).

In contrast, due to bronchoconstriction in asthmatics, the elevated resistance results in an increased mechanical time constant for lung emptying. With increased respiratory rate and existing flow limitation, expiration towards V_r becomes increasingly prolonged and the next inspiration begins before V_r is reached (**Figure 2**).

Additionally, studies in adults have shown, especially when bronchoconstriction is induced acutely (*i.e.,* histamine or methacholine), tonic inspiratory muscle activity remains

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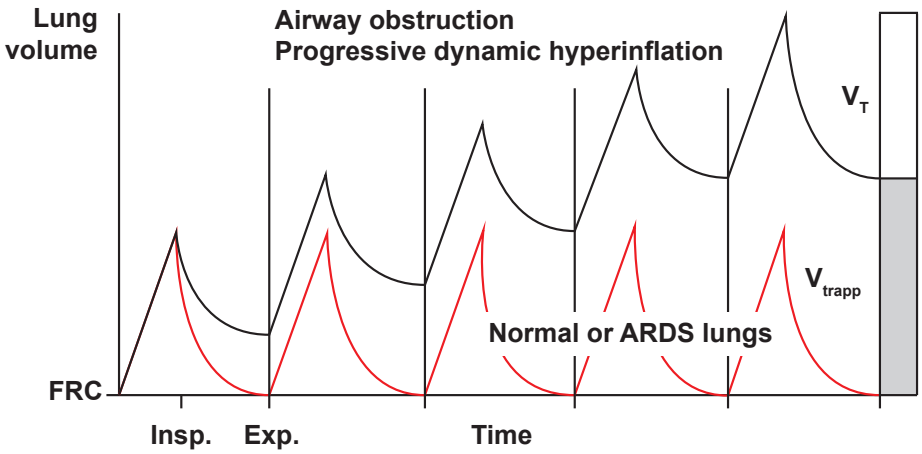

Figure 2. -Dynamic Hyperinflation (Black lines) during an acute asthmatic attack.
-Red lines: normal subjects or ARDS
V_T = Tidal Volume
ti= inspiratory time
te= expiratory time
V_{trapp} = Trapped Volume

throughout expiration and tends to slow it down, contributing to hyperinflation. Similarly, glottic constriction during bronchospasm limits expiration, and contributes to air trapping as well. It should be mentioned that hyperinflation which is developed as a result of acute airflow obstruction during an asthma attack tends to increase airway caliber, reduce airway resistance and improve expiratory flow (**Figure 3**). However, the reduction of airway resistance and the beneficial effect on gas exchange is accomplished at the expense of

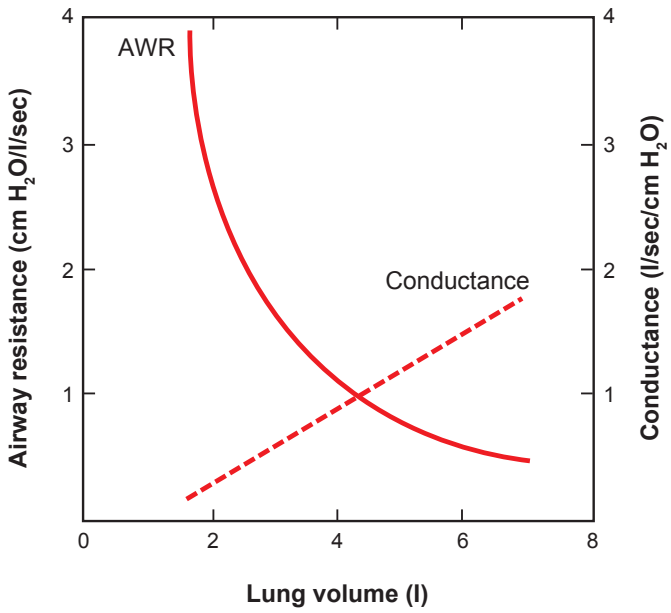

Figure 3. Airway Resistance/Lung Volume curve. Increasing lung volume (hyperinflation) increases the caliber of the airways. Airway resistance (AWR) decreases with increasing lung volume (hyperinflation).

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increased mechanical load of the respiratory muscles.

Early studies of asymptomatic asthmatic children have demonstrated that classic spirometry is not correlated with lung volume abnormalities such as RV, TLC or RV/TLC elevations. In a study of 178 asymptomatic asthmatic children, the RV, TLC or RV/TLC values were abnormally high in 26%, 33% and 41% of these patients respectively, although their forced expiratory volume in 1 second (FEV_1), FEV_1/FVC and forced expiratory flow 25–75% ($FEF_{25-75\%}$) fell within the normal range; indicating that hyperinflation is present even in well-controlled asthma in children. These results were verified in recent studies in preschool children, where the increase of the patient's FRC correlated with the disease severity. It should be mentioned that in the same group of children, a concomitant reduction of compliance was monitored when they were symptomatic. It is worth mentioning that both abnormalities were improved after bronchodilator treatment.

Interestingly, hyperinflation expressed as FRC measurement also was reduced after a six-week treatment in asthmatic preschoolers. Similar results are recorded in a double-blind study of asthmatic children treated with budesonide for 28 weeks. In this study, the reduction of both RV and TLC was evident from the 8th week of treatment. Increased TLC was found also in an early study of Greaves *et al.* in asthmatic adults with childhood onset asthma: the patients of the same study with adult onset asthma had normal TLC values, indicating that episodes of bronchoconstriction in childhood might predispose to changes in the lung that may follow the patient after the remission of the symptoms.

Most asthmatic children, regardless of their severity, seem to have normal lung function; indicating that spirometry parameters are not a sensitive marker of severity in pediatric asthma. On the contrary, as in a recent study of Mahut *et al.* in 160 asthmatic children has shown, 11% of the patients with normal spirometric parameters correlated with small airways (*e.g.,* forced expiratory flow at 50% [$FEF_{50\%}$]) presented hyperinflation. Moreover, from a study by the same group in subjects with asthma of different severity, it was found that although there were no differences in forced expiratory flows of children who experienced severe exacerbation compared to that of their less symptomatic peers, their RV/TLC was higher.

It seems that, as found in adults, hyperinflation might be a sensitive marker of disease severity in children. The above-mentioned studies emphasize the usefulness of the assessment of lung volumes and their response to treatment since they are better indicators of the degree of the small airway disease and hyperinflation, which apparently, cannot be monitored by spirometry.

Only taking the imaging of hyperinflation chest radiographs mostly obtained at TLC into consideration might be misleading regarding the severity of hyperinflation. Moreover, pediatric studies have indicated the relative insensitivity of chest radiographs in the detection of hyperinflation.

Chest HRCTs and MRIs were recently evaluated by a number of studies in adults and children with asthma. The degree of air trapping found on HRCT was correlated with abnormalities of RV, TLC and FRC values and was quantified using CT attenuation values. The quantitative CT was recently evaluated in asthmatic children and was correlated with the TLC% and thoracic gas volume (TGV) parameters. Moreover, in a recent multivariate analysis of risk factors for air trapping using quantitative CT analysis in

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adolescent and adult asthmatics, it was found that factors such as duration of asthma, history of pneumonia, neutrophilic lung inflammation and atopy were independent risk factors for the presence of air trapping.

In conclusion, hyperinflation is present in a high proportion of asthmatic children, is correlated with the disease severity and responds to treatment with bronchodilators and inhaled corticosteroids. Since classic spirometry parameters are poor markers of small airway disease and of the severity of the disease, lung volumes or air trapping quantification by HRCT should be included in the follow up of selected groups of asthmatic children (*e.g.,* difficult-to-treat asthma).

Bronchiolitis

Most children with acute viral bronchiolitis present small airway obstruction and hyperinflation on chest radiograph. Early studies in infants with bronchiolitis have shown that hyperinflation, expressed as TGV (Thoracic Gas Volume) at the end of expiration, was increased in 77% of the patients at the acute phase of the disease, remained detectable in 43% of them after three months and in 17% one year after the initial episode. The values of TGV did not correlate with the respiratory syncytial virus (RSV) isolation, atopy, history of prematurity or the age of the subjects at admission.

Pathophysiologically, the increased airway resistance together with the decreased elastic recoil due to small airway disease or collapse, seem to be the main factors leading to hyperinflation in acute bronchiolitis.

A study in low birth weight preterm infants with a history of respiratory distress syndrome (RDS) at the neonatal period, studied at 10 months of age, recorded both remaining increased airway resistance and air trapping correlated with the severity of bronchoconstriction. The same group found that the symptomatic low birth weight preterm infants with history of RDS have more severe hyperinflation compared with their non-symptomatic peers, indicating correlation of hyperinflation with severity of bronchiolitis.

Recently, scientific interests have focused on recurrent episodes of wheezing bronchiolitis and their link to asthma or COPD in adult life. A recent study in infants and toddlers with a history of at least three episodes of wheezing reported that when the patients were asymptomatic, their lungs presented no evidence of small airway damage or air trapping.

Bronchiolitis obliterans or constrictive bronchiolitis, which is characterized by excessive air trapping, increased lung volumes and a mosaic pattern on HRCT films, is also worth mentioning. Interestingly, a recent study reported many similarities of constrictive bronchiolitis with severe problematic asthma regarding their chest HRCT findings. Children with history of post-infectious bronchiolitis obliterans at the age of three, when evaluated at the age of ten, had hyperinflation and airflow obstruction. It is of interest that their peak aerobic capacity was inversely proportional to the severity of their rest hyperinflation, reduction of activities and/or quality of life (QoL).

Conclusively, children with acute bronchiolitis commonly present hyperinflation correlated with the degree of obstruction, and in most children, remits with age. In bronchiolitis obliterans, hyperinflation is relative to the severity of the disease and the aerobic capacity of the patients and tends to persist for many years.

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Cystic Fibrosis

Cystic fibrosis is a chronic pulmonary disease presented mostly with airway inflammation, progressive obstruction and hyperinflation. Pulmonary hyperinflation may be detected early in life of CF patients and may progress during childhood.

Pathophysiologically, both static and dynamic hyperinflation seem to be consequences of the reported air trapping in CF. In moderate to severe CF, the presence of airway obstruction and the changes in the elastic properties of the lung result in an elevation of the (EELV) at rest (static hyperinflation). During exercise, the respiratory rate increases and V_T expands to cover the elevated needs (**Figure 2**). In CF patients, during worsening of expiratory flow (exacerbation) or increased ventilatory needs (exercise), the decreased elastic recoil pressure and the increased airway resistance result in progressively prolonged expiration leading to elevated EELV (dynamic hyperinflation) with detrimental mechanical effects.

As a recent study has suggested, hyperinflation in CF seems to be recorded very early in life. It was found that nearly 70% of studied infants with CF in their study had elevated FRC.

Various studies have reported a correlation of hyperinflation with the infective pathogen density in distal or smaller airways.

A different group showed that 39% of CF patients aged 6-8 years had hyperinflation, and that this percentage reached 67% by the age of 18 years old.

Interestingly, the group of patients colonized with Pseudomonas aeruginosa presented more profound disease progression. Moreover, the same study recorded that the alterations of the lung function were correlated with specific cystic fibrosis transmembrane conductance (CFTR) genotypes.

The above findings suggest that measurements of lung volume may provide valuable information about disease progression and phenotyping, and evaluate the benefit of antibiotic treatment in CF patients.

Regarding imaging of the CF children with plain chest radiographs, early studies have used scoring systems such as the Brasfield score to quantify pulmonary hyperinflation. Nevertheless, due to the possible overestimation of hyperinflation in chest radiographs, the need for more accurate assessments has evolved. Computed tomography seems to be more sensitive than chest radiographs in CF children. Various low dose techniques and limited slices protocols have been evaluated to overcome the concerns over radiations. At the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF) cohort, CT scans in asymptomatic infants at 3 months of age recorded gas trapping in 67% of the subjects. In contrast, in patients of the London Cystic Fibrosis Collaboration (LCFC) cohort, most of the CT scans were classified as normal, indicating the need for further validation of CT scoring systems in very young infants.

In conclusion, hyperinflation is detected early in the course of CF and is correlated with disease severity, microbial colonization and exercise ability. The above characteristics make the assessment of the degree of hyperinflation profoundly valuable in young CF patients.

Neonatal Chronic Lung Disease (CLD), Primary Ciliary Dyskinesia (PCD), Alpha-1 Antitrypsin (A_1AT) Deficiency

A number of rare childhood pulmonary diseases such as CLD, PCD and A_1AT deficiency may present hyperinflation.

A limited number of studies have indicated that FRC, RV or RV/TLC were increased in infants with history of prematurity and CLD.

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In children with PCD, hyperinflation is recorded as increased RV and RV/TLC. In these children, hyperinflation documented by plethysmography was correlated with the P. aeruginosa infection and HRCT findings. Magnin *et al.* reported that 50% of the PCD children had hyperinflated lungs in HRCT scans.

Hyperinflation has also been reported in a study of children with A_1AT deficiency with liver disease.

In conclusion, most childhood pulmonary diseases either with airway obstruction or lung parenchyma destruction or both, frequently present hyperinflation of varying severity. Hyperinflation is usually correlated with disease severity, predicts the disease progression in a few cases and plays a cardinal role in the pathophysiology of the clinical conditions at rest, exercise and exacerbations. A systematic quantitive assessment of pulmonary hyperinflation in common pediatric diseases such as asthma and CF will enrich our knowledge of pathophysiological mechanisms and improve disease treatment and follow-up.

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CLINICAL

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C.

TREATMENT

C1.
Pharmacotherapy of Lung Hyperinflation

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C1.
Pharmacotherapy of Lung Hyperinflation

Key Points

1.
Bronchodilators of all classes and duration of action have been shown to decrease lung hyperinflation (deflators) and pulmonary gas trapping with reciprocal increases in inspiratory capacity and vital capacity, respectively, in patients with chronic obstructive pulmonary disease.

2.
Bronchodilator-induced reductions in lung hyperinflation at rest and during exercise have beneficial effects on exertional dyspnea, exercise tolerance and health status in chronic obstructive pulmonary disease.

3.
Patients with the greatest lung hyperinflation at rest have the greatest lung deflation improvements in response to a bronchodilator.

4.
A significant bronchodilator response may not be uncovered by evaluation of changes in forced expiratory volume in 1 second, since improvements in lung volumes can often occur independently of changes in maximal expiratory flow rates.

5.
Improvements in dyspnea and exercise tolerance following pharmacological lung volume reduction are closely related to the release of tidal volume restriction and enhanced neuromechanical coupling of the respiratory system.

6.
Dual long-acting muscarinic antagonist/ long acting ß2-agonist bronchodilators (deflators) in a single device have superior effects on hyperinflation compared to mono-components.

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INTRODUCTION

Lung hyperinflation, chronic dyspnea, reduced exercise capacity and physical inactivity are independent predictors of increased mortality in chronic obstructive pulmonary disease (COPD). Therefore, it is no surprise that a major goal of management is to therapeutically reduce lung hyperinflation (deflation) in the hope of improving dyspnea and exercise tolerance. The negative effects of lung hyperinflation in COPD are well established, including direct evidence to support its relationship with activity-related dyspnea and exercise limitation. Indirect evidence of the importance of lung hyperinflation in dyspnea causation and exercise intolerance in COPD comes from multiple studies which have examined therapeutic interventions that reduce or counterbalance the effect of lung hyperinflation. In this regard, pharmacological treatments that reduce resting and/or dynamic lung hyperinflation have the potential to improve dyspnea and exercise capacity, as well as other related clinical outcomes such as health status or even survival.

Bronchodilator therapy

Effects on measurements of lung hyperinflation at rest

Bronchodilators reduce airway smooth muscle tone, reduce airway resistance, improve airflow, and accelerate the mechanical time constants for lung emptying. In this way, inhaled bronchodilators favorably alter the dynamically-determined components of resting lung hyperinflation and help deflate the overinflated lung (**Figure 1**). Bronchodilators of all classes and duration of action have consistently been shown to decrease measurements of lung hyperinflation (functional residual capacity [FRC]) and pulmonary gas trapping (residual volume [RV])

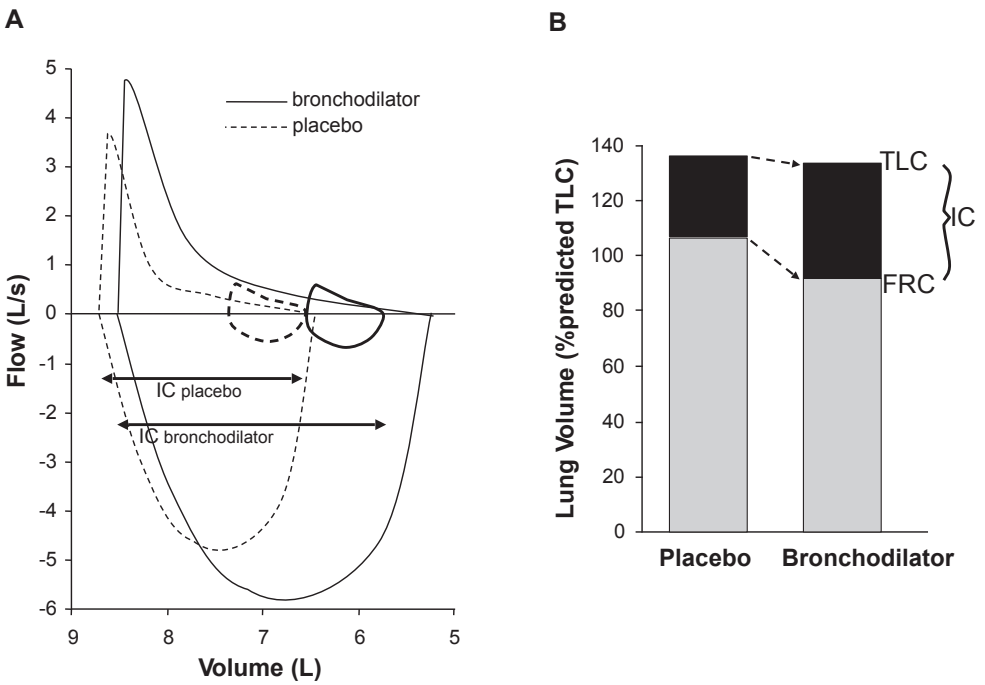

Figure 1. *Typical bronchodilator-induced changes in (A) maximal and tidal flow-volume loops and (B) lung volumes at rest. With a bronchodilator, maximal expiratory flows increase allowing inspiratory capacity (IC) to increase and functional residual capacity (FRC) to decrease. TLC: total lung capacity.*

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with reciprocal increases in inspiratory capacity (IC) and vital capacity (VC) in patients with COPD.

End-expiratory lung volume (EELV) is a term that has been used interchangeably with FRC; however, EELV more accurately reflects the combined dynamic and "static" determinants of this operating lung volume at rest and throughout exercise. Since spirometric measurements are simple to perform, changes in IC have often been used to track changes in EELV both at rest and throughout exercise. However, bronchodilator-induced improvements in IC may underestimate the reduction in resting EELV since total lung capacity (TLC) has been shown to fall by small amounts in the order of 0.1-0.2L. As single agents, both classes of inhaled bronchodilators (beta$_2$-agonists and muscarinic antagonists) have been shown to increase the resting IC in patients with COPD by approximately 0.2-0.4L or 10-15%. The largest post-bronchodilator improvements in IC are seen in patients with the greatest resting lung hyperinflation (*e.g.*, baseline IC<80%pred.). Decreases in lung volume of the magnitude seen in response to bronchodilators are associated with reduced intrinsic mechanical loading and increased functional strength of the respiratory muscles. Such mechanical improvements are particularly important in dyspneic patients with more severe COPD who gain the greatest subjective benefit.

Improvements in forced expiratory volume in 1 second (FEV_1) following a bronchodilator, especially in more advanced COPD, commonly indicate lung volume recruitment (increased VC) as a result of reduced pulmonary gas trapping (decreased RV). Thus, studies have shown a preserved or decreased FEV_1/FVC ratio in response to all classes of bronchodilators. This pattern of lung volume recruitment is noted particularly in patients with more severe lung hyperinflation. Moreover, a lack of change in FEV_1 after bronchodilator treatment does not necessarily reflect a lack of change in lung hyperinflation or associated subjective benefits for the patient.

The combination of a long-acting muscarinic antagonist (LAMA) and a long-acting β_2-agonist (LABA) can have additive effects on reducing lung hyperinflation. Van Noord *et al.* were the first to study the combined effect of two long-acting bronchodilators (tiotropium and formoterol) on IC over a 24-hour period in patients with moderate-to-severe COPD. After the 2-week treatment periods, they confirmed additive effects on lung deflation with significant increases in average daily IC and daytime peak IC with the combination treatment versus tiotropium alone. Importantly, the mechanical benefits were also evident throughout the night. More recent studies have also shown slightly greater improvements in resting lung hyperinflation (increases in IC) with long-acting bronchodilator combinations or fixed-dose dual products (such as indacaterol/glycopyrronium) over tiotropium monotherapy.

Effects on lung hyperinflation during exercise

Bronchodilators do not necessarily abolish expiratory flow limitation in patients with more advanced COPD, but allow patients to generate the same or greater respired flow rates at lower operating lung volumes (deflation). There has recently been interest in measuring increases in IC as a surrogate measure of lung deflation during exercise in response to bronchodilator treatment in COPD. This approach seems reasonable, as there is evidence that TLC and the elastic properties of the respiratory system are not changed by exercise in health or disease. There is also evidence that patients with COPD are able to maximally activate their diaphragm during inspiratory efforts to TLC while exercising. Inhaled bronchodilators have been shown to reduce lung hyperinflation (increase IC) at

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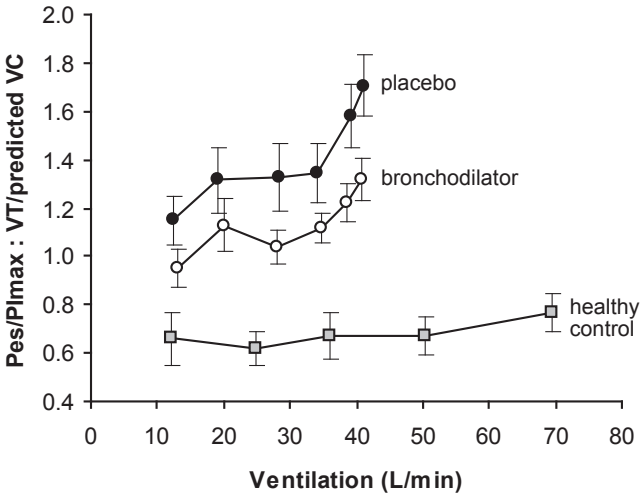

Figure 2. *The ratio between respiratory effort (esophageal pressure relative to maximum [Pes/PI_{max}]) and tidal volume displacement (V_T standardized as a fraction of predicted vital capacity [VC]), an index of neuromechanical dissociation, is shown during exercise after a bronchodilator (tiotropium) versus placebo in COPD compared with a group of age-matched healthy controls. The effort-displacement ratio is increased in COPD compared to normal throughout exercise, with an upward trend towards the end of exercise that did not occur in the healthy subjects. Post-bronchodilator, this ratio was reduced throughout exercise in COPD. From O'Donnell DE, et al. J Appl Physiol 2006; 101: 1025-1035.*

standardized exercise work rates/times and at peak exercise. Such bronchodilator-induced increases in exercise IC have consistently been associated with improvements in exertional dyspnea and exercise endurance time in patients with moderate-to-severe COPD.

The IC indicates the position of tidal volume (V_T) relative to TLC on the sigmoidal pressure-volume relation of the respiratory system. Therefore, a post-bronchodilator increase in IC indicates reduced elastic/inspiratory threshold loading of the inspiratory muscles, an important determinant of dyspnea. An increased IC and lower operating lung volumes allow patients to achieve the required ventilation (V_E) during rest and exercise with reduced contractile muscle effort and at a lower oxygen cost of breathing. By increasing resting IC, bronchodilators (deflators) also increase the available dynamic inspiratory reserve volume (IRV), and thereby delay the onset of critical respiratory-mechanical

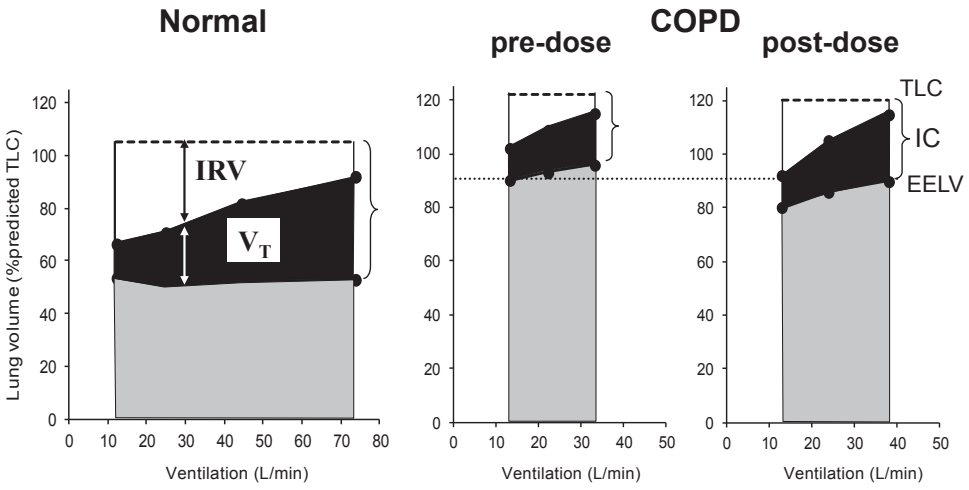

Figure 3. *Operating lung volumes during exercise are shown pre- and post-bronchodilator in COPD compared with healthy normal subjects. Bronchodilators result in an increase in inspiratory capacity (IC) and a parallel downward shift in the end-expiratory lung volume (EELV) over the course of exercise, thus allowing greater expansion of tidal volume (V_T). From Laveneziana P, O'Donnell DE. Dis Manage Health Outcomes 2007; 15(2): 91-100.*

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constraints on V_T expansion (and thereby V_E) during exercise. Thus, throughout exercise, less respiratory muscle effort is required to achieve greater tidal volume expansion: the dissociation between central respiratory drive and the mechanical response of the respiratory system is partially reversed. Improvements in dyspnea and exercise tolerance are closely related to this release of V_T restriction and enhanced neuromechanical coupling of the respiratory system. Thus, for any given exercise intensity or ventilation, patients breathe on the more linear portion of the respiratory system's pressure-volume curve, which delays the onset of neuromechanical dissociation and the attendant dyspnea (**Figure 2**).

Dynamic lung hyperinflation (DH) is defined as the acute (temporary) increase in EELV (or decrease in IC) relative to resting values. The rate of DH is often not changed by administration of a bronchodilator, possibly due to the higher levels of V_E that can be achieved secondary to the release of V_T restriction that occurs with lung deflation. In other words, bronchodilators result in a parallel downward shift in the EELV over the course of the exercise test/task, reflecting the reduction in resting lung hyperinflation (**Figure 3**). The physiological effects of pharmacological lung volume deflation are summarized in **Table 1**.

- Reduced respiratory muscle load.
- Increased inspiratory muscle strength.
- Enhanced neuromechanical coupling.
- Delayed ventilatory limitation to exercise.
- Reduced exertional dyspnea.
- Improved cardiac function.

Table 1. *Beneficial effects of lung deflation.*

Effects on activity-related dyspnea and exercise endurance

Randomized controlled trials have examined the effects of LABA, LAMA and LABA/LAMA combinations on dyspnea intensity ratings during exercise and/or dyspnea related to activities of daily living in patients with moderate-to-severe COPD. Bronchodilator-

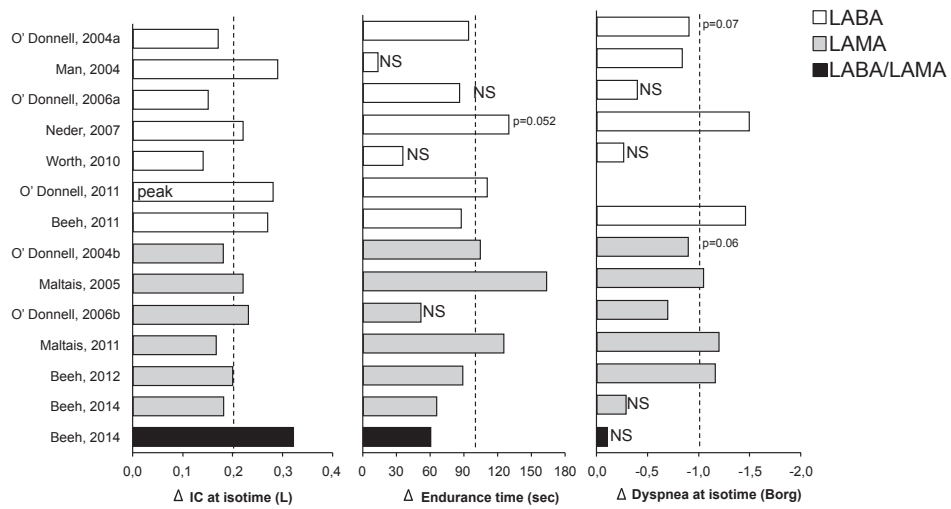

Figure 4. *Improvements in response to long-acting beta2-agonists (LABA), long-acting muscarinic antagonists (LAMA) and LABA/LAMA combinations compared with placebo are shown for exercise measurements of inspiratory capacity (IC) at a standardized time during exercise (isotime), constant-work rate cycle exercise endurance time, and dyspnea intensity ratings at isotime. Treatment differences in these randomized, placebo-controlled studies are statistically significant (p<0.05) unless indicated otherwise. NS: not significant.*

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induced improvements in perceived dyspnea intensity during constant work rate cycle exercise are variable, possibly due to measurement variability in this outcome, as well as the modest numbers of patients in many of these studies (**Figure 4**). Despite variability in improvements in exertional dyspnea, increases in IC at a standardized time near end-exercise (isotime) and in exercise endurance time with long-acting bronchodilators compared with placebo appear to be more consistent (**Figure 4**). Increases in cycle exercise endurance time in response to bronchodilator therapy are in the order of 20% on average. Such increases in cycling endurance time are typically within the range that is thought to be clinically important, *i.e.,* about 100 seconds. It is possible that LABA/LAMA fixed-dose combinations may extend the improvements seen with single agents; however, there is currently limited information on exercise responses with dual bronchodilator therapy.

The effects of long-acting bronchodilators on the Transition Dyspnea Index (TDI) are shown in **Figure 5**. Although variability in this outcome is evident, the improvements in TDI total scores were approximately 1.0 unit compared with placebo, which corresponds to the minimal clinically important difference (MCID). Recent studies show that two approved combinations of a LABA and a LAMA in a single dry powder inhaler provided significant and clinically meaningful improvements in TDI total scores compared with placebo at six weeks and at 24 weeks. In these studies, the magnitude of improvement in the TDI with dual bronchodilators was numerically greater than with a single bronchodilator, but only marginally or not statistically significant.

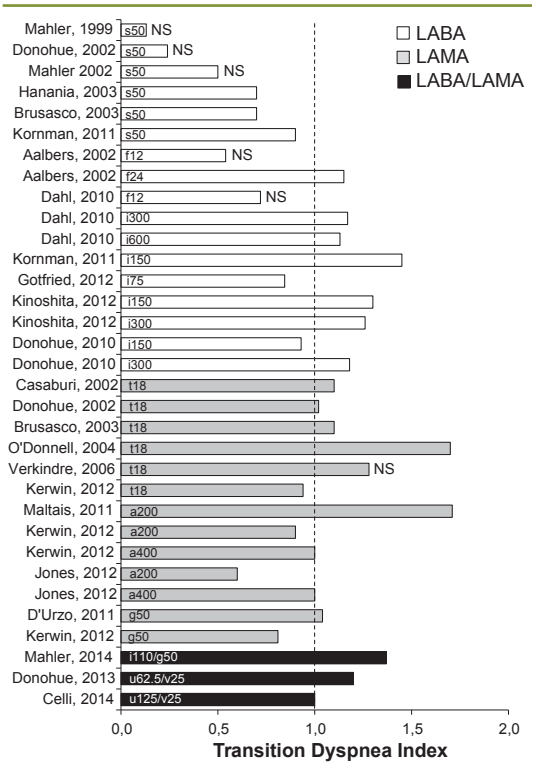

Figure 5. *Treatment differences for the Transition Dyspnea Index (TDI) measured in response to long-acting beta2-agonists (LABA), long-acting muscarinic antagonists (LAMA) and LABA/LAMA combinations compared with placebo. The dashed line represents the accepted minimal clinically important difference (MCID) of 1 unit. Treatment differences in these randomized, placebo-controlled studies are statistically significant ($p<0.05$) unless indicated otherwise. NS: not significant. Drugs and dosages shown are as follows: s50, salmeterol 50 µgb.i.d.; f12 and f24, formoterol 12 and 24 µgb.i.d.; i75, i150, i300 and i600, indacaterol 75, 150, 300 and 600 µg once daily; t18, tiotropium 18 µg once daily; a200 and a400, aclidinium 200 and 400 µg b.i.d.; g50, glycopyrronium 50 µgonce daily; i110/g50, indacaterol/glycopyrronium 110/50 µg once daily; u62.5/v25 and u125/v25, umeclidinium/vilanterol 62.5/25 and 125/25 µg once daily.*

Effects on physical activity and health status

There is considerable interest in evaluating the impact of modern pharmacotherapy on increasing physical activity in COPD. While pharmacological lung volume deflation is consistently associated with improved exercise capacity, translation to improved functional status and spontaneous increases in habitual physical activity does not necessarily follow. Thus, inactivity in COPD is multifactorial, and in many patients, ventilatory limitation and

dyspnea (which are delayed by bronchodilator therapy) may not be the dominant exercise-limiting symptoms that underscore habitual inactivity. Recent studies which have examined the impact of bronchodilator therapy on physical activity (measured by activity monitors) have yielded variable results that are difficult to interpret. It seems likely that additional behavioral modification, preferably in the context of pulmonary rehabilitation, is required to achieve sustained improvements of this important clinical outcome in individual patients.

Any intervention that can improve respiratory symptoms or the ability to perform activities is also likely to improve disease-specific health status and quality of life. The St. George's Respiratory Questionnaire (SGRQ) is a standardized index of health status that is commonly used as an outcome measure in pharmacological studies in patients with COPD. Treatment changes in SGRQ total score in response to long-acting bronchodilators tend to fall at or below the level thought to be clinically meaningful, *i.e.*, -4 units (**Figure 6**).

ICS and ICS/LABA combinations

Most large randomized clinical trials evaluating the efficacy of inhaled corticosteroid (ICS) and LABA combination therapy have been designed to evaluate simple spirometry, exacerbations or health status as primary outcome measures. Several studies have reported activity-related dyspnea as a secondary outcome and have shown consistent improvements with ICS/LABA therapy compared to a placebo; however, only a few have shown significant benefit when compared to its LABA component.

The combination of an ICS with a bronchodilator has been shown to have beneficial effects on resting IC compared to placebo. The fluticasone/salmeterol combination was shown to reduce resting and dynamic hyperinflation, as well as to increase exercise endurance time compared to placebo, but not vs. salmeterol. The budesonide/formoterol combination was reported to reduce resting and dynamic hyperinflation and increase exercise endurance compared to both placebo and formoterol. A more recent study found that fluticasone/salmeterol increased IC at rest and throughout exercise in patients with mild-to-moderate COPD, but without

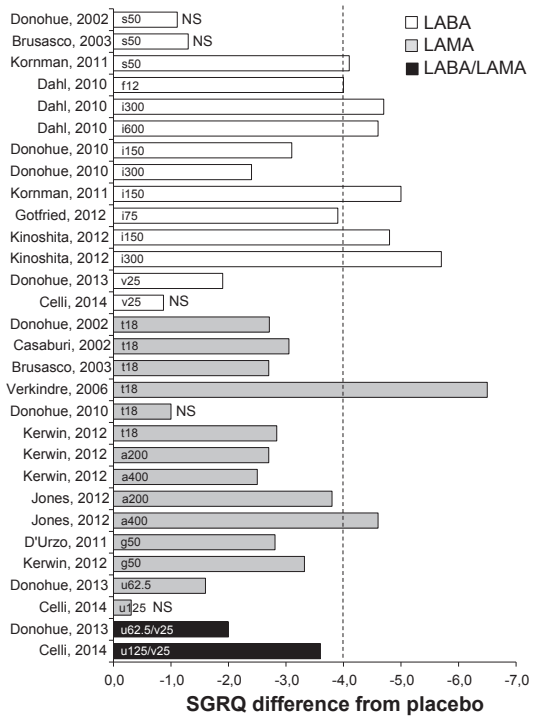

Figure 6. *Treatment differences for the St. George's Respiratory Questionnaire (SGRQ) total score measured in response to long-acting beta2-agonists (LABA), long-acting muscarinic antagonists (LAMA) and LABA/LAMA combinations compared with placebo. The dashed line represents the accepted minimal clinically important difference (MCID) of 4 units. Treatment differences in these randomized, placebo-controlled studies are statistically significant ($p<0.05$) unless indicated otherwise. NS: not significant. Drugs and dosages shown are as follows: s50, salmeterol 50 µgb.i.d.; f12, formoterol 12 µgb.i.d.; i75, i150, i300 and i600, indacaterol 75, 150, 300 and 600µg once daily; t18, tiotropium 18 µg once daily; v25, vilanterol 25 µg once daily; a200 and a400, aclidinium 200 and 400 µg b.i.d.; g50, glycopyrronium 50 µg once daily; u62.5/v25 and u125/v25, umeclidinium/vilanterol 62.5/25 and 125/25 µg once daily.*

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consistent improvements in dyspnea intensity or exercise endurance. This is not surprising, since increased leg discomfort was a dominant exercise-limiting symptom during the baseline test in this group of patients with milder disease severity.

The beclomethasone/formoterol combination has been reported to improve resting lung volumes more than fluticasone/salmeterol. In addition, the budesonide/formoterol combination was found to show a faster rate of onset than fluticasone/salmeterol combination or formoterol alone. The bronchodilator combination of tiotropium and salmeterol was more effective than fluticasone/salmeterol for improving resting lung volumes in hyperinflated COPD patients, although exercise endurance time was not significantly different between these treatment combinations.

When ICS is given as monotherapy, small improvements in airway function have been shown compared with placebo. Inhaled corticosteroid monotherapy added to a foundation of long-acting bronchodilator therapy has also been shown to decrease lung hyperinflation at rest and during exercise, and to improve exercise endurance. The mechanism for an effect of ICS on hyperinflation is unclear, but may involve a direct local action on the micro-vasculature of the airway mucosa, e.g. vasoconstriction. Inhaled extra-fine particles targeting the peripheral lung are a particularly attractive strategy to pharmacologically deflate patients with COPD, as increased small airway resistance is a key mechanism of air trapping in these patients. An extra-fine combination of budesonide and formoterol, which has been shown to result in high and homogenous deposition rates in the airways, has been shown to be superior to a regular-size fluticasone plus salmeterol combination in reducing residual volume and dyspnea scores in hyperinflated COPD patients. Interestingly, FVC increased to a greater extent with this combination than budesonide/formoterol and formoterol alone, and FEV_1 increased more than with a fluticasone/salmeterol combination in two larger randomized clinical trials. These data suggest that part of the deflating effects of inhaled ICS/LABA combinations might be due to the anti-inflammatory effects of the ICS in the small airways. More head-to-head comparisons with detailed physiological measurements will however be necessary for any definitive conclusions.

Other pharmacotherapies

Chrystyn *et al.* (Br Med J 1988) were the first to show a dose-response relationship between oral theophylline administration and reduction in FRC. Theophylline has been reported to improve lung volumes and exercise endurance, possibly through improved respiratory muscle performance secondary to unmeasured lung volume reduction.

The oral phosphodiesterase-4 (PDE4) inhibitor, roflumilast, was associated with progressive improvements in resting airway function, but not in resting lung hyperinflation compared with placebo after 12 weeks of treatment. Roflumilast treatment had small but consistent effects on air trapping during exercise (IC increased by 0.12L at isotime compared with placebo; p=0.008), but this was not sufficient to improve dyspnea or exercise endurance time.

Treatment with the mucoactive/antioxidant n-acetylcysteine (NAC) has been shown to have beneficial effects on small airway function and air trapping. One study in stable patients with moderate-to-severe COPD showed improvements in post-exercise measurements of lung hyperinflation (IC, RV/TLC) and modest increases in cycle exercise endurance time following 6 weeks of treatment with NAC compared with placebo. Another study showed significant improvements in small airway function and exacerbation frequency after 1 year of NAC treatment in patients with stable COPD,

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but failed to demonstrate any improvement in IC, in exercise performance measured by the 6-minute walk test, or in dyspnea measured by the modified MRC dyspnea scale.

SUMMARY

Over-reliance on FEV_1 as the main outcome measure for the evaluation of bronchodilator efficacy in clinical trials has resulted in underestimation of beneficial clinical effects in many patients. In this context, important decreases in lung hyperinflation can occur in the setting of minor or no changes in traditional spirometry, especially in patients with more severe airway obstruction. Pharmacological lung volume reduction (deflation) provides a solid mechanistic rationale for observed improvements in dyspnea and exercise tolerance in COPD. All classes of short- and long-acting bronchodilators (deflators) have been shown to consistently reduce lung hyperinflation across the continuum of COPD, with attendant improvements in exercise endurance and perceived health status. More recently, dual LABA/LAMA bronchodilators delivered in a single device have been shown to have superior effects on lung deflation compared with the mono-components. The expectation is that such sustained improvements in respiratory mechanics will lead to long term improvements in dyspnea and physical activity and, ultimately, to improved health status over a longer life duration.

References of Figure 4, 5, 6 are cited at the end of the book

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Key Points

1.
Several non-pharmacological treatment options are available that can help to either 1) directly reduce dynamic hyperinflation; 2) indirectly improve dynamic hyperinflation by reducing ventilatory needs for a given level of exertion or 3) assist the overburdened respiratory muscles to better cope with the increased loads and improve symptoms during exertion.

2.
Decreases in ventilatory demands with exercise training and oxygen supplementation in some patients result in less dynamic hyperinflation for a given work rate and better tolerance to physical exertion.

3.
In addition to variable effects on resting lung hyperinflation, heliox breathing can decrease the rate of dynamic hyperinflation for a given level of ventilation in selected patients.

4.
Pressure-generating capacity of the overburdened inspiratory muscles can be passively (via non-invasive ventilatory support) or actively (via inspiratory muscle training) improved with beneficial effects on dyspnea in selected patients.

5.
Several simple breathing strategies (e.g. pursed lips breathing, active expiration, and body positioning techniques) that are sometimes used spontaneously may be taught to patients to improve symptoms at rest and during exercise.

6.
Subjective benefits in terms of dyspnea improvement during exertion need to be evaluated in individual patients and weighed against the costs, risks, and time investment of the different interventions.

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INTRODUCTION

Lung hyperinflation is highly prevalent in patients with chronic obstructive pulmonary disease (COPD) and occurs across the continuum of the disease. A growing body of evidence suggests that lung hyperinflation contributes to dyspnea and activity limitation in COPD, and is an important independent risk factor for mortality and disease exacerbations. Important negative consequences of dynamic hyperinflation (DH) during activities include: 1) limits on tidal volume (V_T) expansion, resulting in early ventilatory mechanical limitation; 2) increased elastic and threshold loading on the inspiratory muscles, resulting in increased work and oxygen cost of breathing (reduced efficiency); 3) functional inspiratory muscle weakening due to mechanical disadvantage (i.e., operating at shorter lengths) and increased velocity of shortening needed to generate higher inspiratory flow; 4) negative impact of increased inspiratory muscle work on leg blood flow and muscle fatigue; 5) carbon dioxide (CO_2) retention; and 6) adverse effects on cardiac function and central hemodynamics.

The growing disparity between increased central neural drive and the reduced respiratory muscular / mechanical response due to hyperinflation contributes importantly to the perception of respiratory discomfort during exertion. In this chapter, the physiological rationale and efficacy of selected non-pharmacological interventions aimed at improving symptoms caused by these alterations will be discussed. Several non-pharmacological treatment options are available that can help to either 1) directly reduce dynamic hyperinflation during activities (heliox breathing); 2) indirectly improve dynamic hyperinflation by reducing ventilatory needs for a given level of exertion (exercise training and oxygen); or 3) assist the overburdened respiratory muscles to better cope with the increased loads and improve symptoms during exertion (breathing exercises and non-invasive ventilatory support).

Exercise Training

Rehabilitative exercise training improves exercise capacity and reduces symptoms of dyspnea in patients with COPD. The improvements observed in constant load cycling tasks after properly conducted exercise training programs are larger than those observed with any other intervention. Several physiological and psychological factors have been proposed to explain these improvements. Reduction in DH has been put forward as one of them. There are indications that improvements in the affective perception of dyspnea can also occur without changes in dynamic respiratory mechanics.

It is generally accepted that exercise training does not have an impact on resting pulmonary mechanics. Exercise training primarily reduces ventilatory needs for a given level of exertion and thereby reduces DH for a given work rate. This reduction in ventilatory needs is probably mainly related to improvements in peripheral muscle function after training, with accompanying reductions in reliance on anaerobic metabolism during exercise. Reducing ventilation will allow patients to decrease their breathing frequency, increase VT and reduce end-expiratory lung volume (EELV) for a given workload, and thereby result in reduced symptoms of dyspnea and improved exercise endurance. A larger VT will result in a decreased dead space/VT ratio, thus further reducing the ventilatory requirements during exercise. For a given level of ventilation, EELV does not seem to be altered after exercise training.

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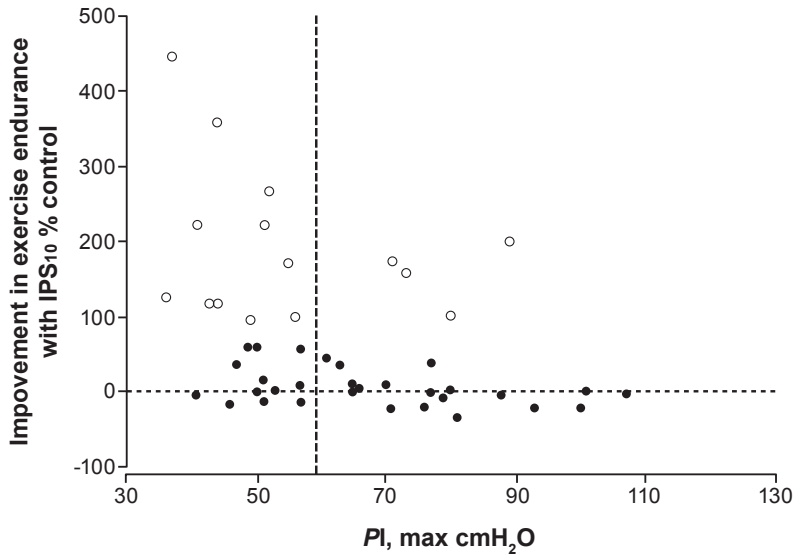

Figure 1. *Relationship (r=-0.49, p=0.001) between improvement in exercise endurance and maximal inspiratory pressure (PI,max). IPS10: inspiratory pressure support of 10 cmH_2O. • patients with a change in exercise endurance <100%; • patients with a change in exercise endurance of ≥100% (at least doubled). The vertical dashed line helps illustrate that most responders had severely reduced pressure generating capacity of inspiratory muscles (PI,max<60cmH20). Adapted from: van 't Hul A et al. Acute effects of inspiratory pressure support during exercise in patients with COPD. Eur Respir J 2004;23(1):34-40.*

Although the evidence for exercise training is strong, there exists a proportion of patients who do not achieve meaningful gains in exercise capacity after this intervention. These patients are characterized by more severe expiratory flow limitation and profound ventilatory limitation during exercise, resulting in severe symptoms of dyspnea. Several other treatment options are available that might be useful to alleviate the negative consequences of DH during exercise.

Non-invasive Ventilatory Support

The use of non-invasive ventilation (NIV) consistently increases endurance time and reduces dyspnea perception during constant load cycling tasks in selected patients with COPD. Assisting ventilation by either continuous positive airway pressure (CPAP) or inspiratory pressure support (IPS) does not directly improve hyperinflation at rest or the increase in EELV during exercise. Improvements in exercise capacity in response to these interventions are likely achieved by unloading the inspiratory muscles during exercise, thus improving the demand/capacity imbalance of the respiratory muscles. This is supported by data showing that patients with pronounced inspiratory muscle weakness are more likely to achieve larger improvements in exercise endurance (**Figure 1**). Optimal CPAP counterbalances intrinsic positive end-expiratory pressure (PEEPi), thereby minimizing the elastic threshold load on the inspiratory muscles, while IPS provides variable resistive and elastic unloading of ventilatory muscles during exercise. Unloading of the respiratory muscles by proportional assisted ventilation (PAV) has been shown to improve leg blood flow and exercise performance during sustained high intensity exercise in healthy trained cyclists. In patients with COPD,

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respiratory muscle unloading by PAV during a relatively short constant load cycling task showed positive effects on endurance time, leg muscle oxygenation, and dyspnea and leg fatigue symptoms. Reductions in leg muscle fatigue after exercise in response to unloading the inspiratory muscles by combining PAV with heliox has also been shown. These data support the hypothesis of a competition between limb and respiratory muscles for the available O_2 delivery during exercise. These interventions require individual guidance and full supervision if they are implemented in clinical practice (e.g., during an exercise training intervention) and are not tolerated well by all patients. These factors need to be taken into account when considering the implementation of these interventions into rehabilitation interventions.

Several small randomized clinical trials (RCTs) have demonstrated that the addition of NIV to an exercise training program in COPD can result in higher training intensities and larger improvements in exercise capacity. A meta-analysis published in the Cochrane library (Menadue C) quantified the improvement in endurance exercise capacity by an average of 59% in two studies that provided NIV during training, compared with training without NIV or training with sham NIV. Acute improvements in exercise endurance are more consistent when using inspiratory pressure support than other ventilator modes. This, together with its relative ease of use, suggests that this method is probably the first choice for NIV-assisted training. Time requirements and required expertise in implementation and titration will likely limit the practical use of this adjunct to a few centers.

Manipulations of Inspired Gas Delivery

Supplemental O_2 during exercise has been shown to consistently improve exercise capacity and to reduce ventilation and

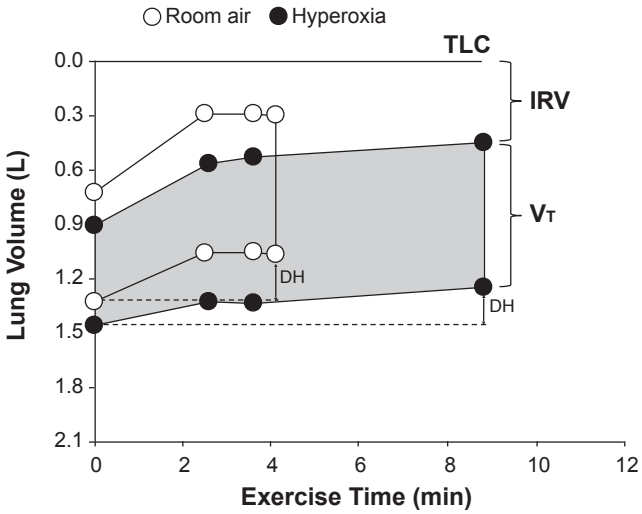

Figure 2. *Operating lung volumes are shown during constant work rate cycle exercise in COPD patients during hyperoxia versus room air breathing. End-expiratory (EELV) and end-inspiratory lung volumes (EILV) were reduced at rest (0 min) and throughout exercise during hyperoxia compared to room air breathing. The magnitude of dynamic hyperinflation (i.e., the difference in EELV from resting values) was similar at peak exercise during hyperoxia compared with room air in a hypoxemic patient with COPD. IRV, inspiratory reserve volume; TLC, total lung capacity; V_T, tidal volume.*
Adapted from: Guenette JA et al. Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulm Med 2013; e956081.

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breathlessness at a standardized time (isotime) during exercise testing in COPD patients with and without resting hypoxemia. O_2 supplementation during exercise delays ventilatory limitation and accompanying dyspnea mainly by reducing ventilatory demand. O_2 supplementation has variable effects on DH and reduced DH is not a prerequisite for dyspnea relief (**Figure 2**). Both improved oxygen delivery to the peripheral muscles (resulting in less reliance on anaerobic metabolism) with altered afferent inputs from leg muscle mechanoreceptors, and attenuated peripheral chemoreceptor stimulation are possible explanations for the reduction in ventilatory demand for a given level of exertion. Despite the good physiological rationale supporting the use of this intervention, six out of seven published RCTs failed to demonstrate an additional benefit of oxygen supplementation on training benefits in patients with COPD. Only one well-designed study by Emtner and colleagues documented higher work rates during training in the oxygen group, which consequently resulted in larger improvements in exercise capacity. The latest American Thoracic Society/European Society statement on pulmonary rehabilitation (Spruit et al.) suggests that individualized oxygen trials should be used to identify patients who might benefit from oxygen supplementation during exercise training.

Heliox is a low density gas mixture (79% helium, 21% oxygen) that has been used in patients with COPD to reduce airflow resistance during the increasing ventilatory needs of exercise. Heliox supplementation has been shown to improve exercise performance in patients with COPD in comparison with room air breathing. Studies evaluating shortness of breath at a standardized time (isotime) during an endurance cycling task have also consistently shown significant reductions in dyspnea perception. Heliox breathing increases the size of the maximal resting flow-volume envelope and seems to actually slow down the increase in EELV during exercise by decreasing airflow resistance, thereby directly altering DH. Improvements in exercise capacity were correlated with the magnitude of changes in EELV during exercise. In three studies, the response to hyperoxic helium (60-70% helium, 30-40% oxygen) and oxygen supplementation alone was compared during a constant load cycling task in patients with moderate (non-hypoxemic), severe, and very severe (patients on long term O_2 therapy) symptoms. These studies all found significant differences in endurance time in favor of the hyperoxic helium group. They further demonstrated reductions in the resistive work of breathing and reductions in exercise-induced DH in comparison with hyperoxia alone. Three RCTs have investigated the effects of heliox as an adjunct during exercise training in COPD with conflicting results. The complexity of applying helium gas mixtures during exercise training, together with the added expense and lack of conclusive clinical benefits, suggests that, despite the strong physiological rationale, this therapy currently does not play a routine role in pulmonary rehabilitation.

Breathing Exercises

Deep and slow breathing

Training patients to transiently breathe slowly and deeply during exercise has been hypothesized to decrease hyperinflation, work of breathing, and improve symptoms and exercise capacity. Some patients with severe airflow obstruction and lung hyperinflation spontaneously use pursed lip breathing (PLB) to reduce expiratory flow and slow

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down respiratory rate in conjunction with improvements in dyspnea both at rest and during exercise. Patients who do not adopt PLB spontaneously show variable responses. During PLB, patients perform a moderately active expiration through half-opened lips, thereby inducing expiratory mouth pressures of about 5cmH_2O. It has been shown that slowing down expiratory flow reduces the tendency of airways to collapse as well as the resultant air trapping. This is probably the reason why this technique seems to be most effective in patients with severe loss of lung elastic recoil pressure and tracheobronchial collapse. Adopting PLB at rest reduces breathing frequency and increases VT, while ventilation is usually maintained or slightly reduced. Reducing dead space and improving alveolar ventilation in this way likely explains the improvements in gas exchange that are typically observed. These effects have also been observed when a slower and deeper breathing pattern was adopted without using PLB. In a small study Pomidori, L. et al., teaching COPD patients yoga breathing resulted in a slower, deeper pattern of breathing and improvements in oxygen saturation with no increases in symptoms. Effects of long-term breathing retraining interventions on changes in spontaneous ventilatory pattern are still lacking. Data from Bianchi and colleagues obtained by using optoelectronic plethysmography, contribute to our understanding as to why not all patients with COPD obtain symptom relief from PLB (and thus do not spontaneously use it). They observed that reductions in breathing frequency and increases in VT during PLB were achieved by either increasing or decreasing EELV. The group that hyperinflated during PLB (n=19) did not perceive symptomatic benefits, whereas patients who decreased their EELV (n=11) did. Reductions in EELV were positively correlated with improvements in Borg Dyspnea scores ($r=0.71$, $p<0.001$) and with a greater level of expiratory flow limitation ($r=0.45$, $p<0.02$).

Pursed lip breathing during exercise has only been studied in few small studies, with mixed results in terms of dyspnea reduction and improvements in exercise capacity. Spahija and colleagues performed the only study (n=8) that measured changes in EELV and respiratory muscle effort after PLB during constant work bicycle exercise. They found a strong correlation between changes in dyspnea sensation during exercise and both changes in EELV ($r2=0.82$, $p=0.002$) and inspiratory muscle effort ($r2=0.84$, $p=0.001$) occurring with PLB. Interestingly, while all patients reduced their breathing frequency during PLB, only two out of eight subjects were able to reduce their EELV and to decrease their inspiratory effort. These were also the only patients who perceived improvements in dyspnea during exercise. Patients who increased their EELV during PLB experienced worsening of symptoms. Reductions in EELV with PLB again seemed to be related to levels of static hyperinflation (more hyperinflated patients tended to improve more) but the sample size was too small to demonstrate a statistically significant relationship ($r=0.54$, $p=0.17$). Further research is needed to identify and select patients who might benefit from PLB during exercise. It will also be important to standardize the technique and to define the amount of training, instruction and reinforcement needed to apply it successfully.

Collins and colleagues used a computerized ventilation feedback intervention aimed at slowing respiratory rate during exercise, in combination with an exercise training program. They showed reductions in respiratory rate, ventilation and DH at isotime during a constant

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load cycling task. These improvements were related to improvements in dyspnea during exercise. Feasibility and persistence of the these positive effects in the absence of the feedback still need to be determined in order to make this approach applicable for clinical practice.

Active expiration

In healthy subjects, active expiration is not present during resting breathing and only occurs with increased ventilation (e.g., physical activity). In patients with COPD, abdominal muscle activity is often present during resting breathing and this occurs more often in patients with more severe airflow obstruction. Contraction of abdominal muscles increases abdominal pressure during active expiration. It has been hypothesized that, while this increase in abdominal pressure is unlikely to facilitate lung emptying or contribute to lowering of EELV, it should result in lengthening of the diaphragm, thereby optimizing its end-expiratory length tension characteristics.

Diaphragm displacement and its contribution to tidal volume during resting breathing has been shown not to be different in COPD patients in comparison to healthy subjects. Recently, it was also demonstrated that increased expiratory muscle activity in patients with COPD was accompanied by preserved dynamic diaphragm function in comparison with healthy controls during exercise. In patients with very severe airflow obstruction and hyperinflation, the contribution of the diaphragm during exercise was reduced.

It is not clear whether the spontaneously present activity of expiratory muscles should be further stimulated in patients with COPD. Reybrouck and colleagues observed larger decreases in functional residual capacity (FRC) and improvements in pressure generating capacity of inspiratory muscles in patients performing active expiration with electromyography feedback compared to patients who received instructions without myofeedback. Symptomatic benefits were unfortunately not assessed and no studies on the effects of active expiration training during exercise have been performed so far. Casciari and colleagues studied a range of breathing retraining strategies including PLB and active expiration techniques and found additional improvements in exercise capacity in those patients who performed their rehab program in combination with breathing retraining strategies. The relative contribution of each of the different components of the breathing retraining program to the observed benefits is, however, unclear. Dodd et al. studied the effects of a belt strapped around the abdomen to improve length-tension characteristics of the diaphragm during exercise. While this intervention resulted in improved maximal transdiaphragmatic pressure generation it increased relative load on the diaphragm and the diaphragmatic tension time index during exercise and decreased endurance time on the bicycle in comparison with unstrapped exercise.

In summary, spontaneous activity of the abdominal muscles is, depending on the severity of hyperinflation and expiratory flow limitation, often already present at rest in patients with COPD and probably helps to preserve diaphragmatic function during rest and exercise. Whether further improvements in diaphragmatic function after stimulated active expiration can result in improvements in dyspnea and exercise capacity needs to be further explored.

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Body positioning techniques

A forward leaning posture is (analogous to active expiration and PLB) often spontaneously used by patients in an attempt to decrease dyspnea, possibly by improving the length-tension relationships of the diaphragm. Relief of dyspnea is often experienced by patients in the forward leaning position. Patients with pronounced hyperinflation or even paradoxical abdominal movements during inspiration have been shown to perceive the greatest relief of dyspnea in this position. Forward leaning is associated with a significant reduction in electromyographic activity of scalene and sternocleidomastoid muscles, an increase in pressure generating capacity of inspiratory muscles and diaphragm efficiency (**Figure 3**), and significant improvements in thoraco-abdominal movements. In addition, forward leaning with arm support allows accessory muscles (pectoralis minor and major) to significantly contribute to rib cage elevation. Use of a rollator while ambulating allows forward leaning with arm support, decreases dyspnea, and increases exercise capacity.

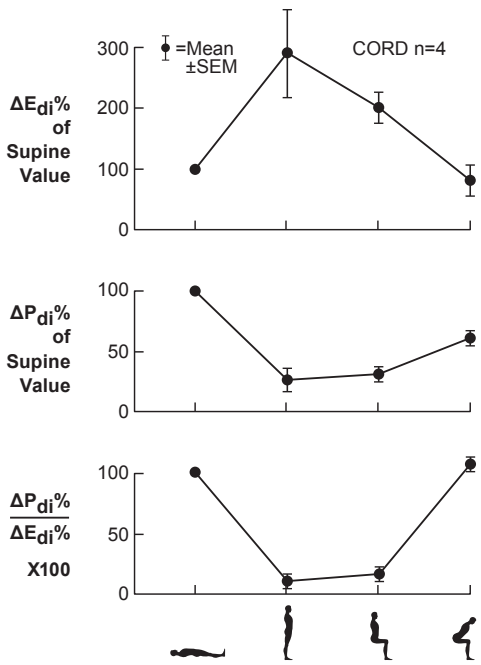

Figure 3. *Mean data for 4 subjects with COPD in supine, standing, erect sitting, and forward leaning position. ΔEdi = inspiratory phasic change in diaphragmatic electromyograph; ΔPdi = inspiratory phasic change in transdiaphragmatic pressure. The ratio ΔPdi%/ΔEdi% is an index of the efficiency of the diaphragm.*
Adapted from: Druz WS and Sharp JT. Electrical and mechanical activity of the diaphragm accompanying body position in severe chronic obstructive pulmonary disease. Am Rev Resp Dis 1982; 125:275-280.

Diaphragmatic breathing

Several studies have described an increase in rib cage contribution to chest wall motion and/or asynchrony between rib cage and abdominal motion in patients with COPD that correlates with airflow obstruction and hyperinflation of the rib cage. During diaphragmatic breathing, patients are instructed to move the abdominal wall predominantly during inspiration and to reduce upper rib cage motion. This aims to: 1) improve chest wall motion and the distribution of ventilation; 2) decrease the contribution of rib cage muscles to the energy cost of breathing; and 3) improve dyspnea and exercise performance. It has been consistently shown that patients with COPD are able to voluntarily change their breathing pattern and to use more abdominal movement and less thoracic excursion during diaphragmatic breathing. Diaphragmatic breathing however often results in more asynchronous breathing movements and has not been shown to improve breathing pattern and ventilation distribution. In most patients, mechanical efficiency of breathing has decreased, whereas work and oxygen cost of breathing has increased, resulting in worsening of dyspnea. In summary, there is no evidence from controlled studies to support the use of diaphragmatic breathing in hyperinflated patients with COPD.

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Inspiratory Muscle Training (IMT)

Strengthening of the inspiratory muscles by specific training programs has been applied frequently in patients with COPD to alleviate dyspnea symptoms and improve exercise capacity. The rationale for IMT is to compensate for the negative consequences of dynamic hyperinflation on the demand/capacity imbalance of the already compromised respiratory muscles. Inspiratory muscle training has been shown to improve inspiratory muscle function (both pressure generating capacity and endurance) and to reduce dyspnea and improve exercise capacity when applied as a stand-alone intervention with controlled training loads. The intervention seems to be most effective in patients with compromised inspiratory muscle function. Effects on dyspnea symptoms and exercise capacity when combining IMT with an exercise training intervention remain inconclusive. In this context, it should be noted that additional effects of other interventions exerting acute physiological effects during exercise testing (e.g., heliox or oxygen supplementation, and assisted ventilation techniques) have also been difficult to establish when combining them with an exercise training program. Larger studies will be needed to show additional effects of interventions that are combined with exercise training since the latter is by itself already a very effective intervention.

Significant enhancement in the velocity of inspiratory muscle shortening during resistive breathing tasks and increases in the size of type II muscle fibres following IMT have been previously observed in patients with COPD. These improvements might be of clinical relevance to patients with respiratory muscle weakness secondary to lung hyperinflation, since improved muscle performance characteristics may improve dynamic function during exercise. Similar to non-invasive ventilator support, IMT is not likely to directly affect hyperinflation at rest or the increase in EELV during exercise. Improvements in dyspnea during exercise in response to IMT and NIV are likely related most to adjustments in the demand/capacity imbalance in the setting of high inspiratory muscle work and functional weakening induced by DH. However, detailed measurements of inspiratory muscle function during exercise in response to IMT have not yet been performed. The beneficial effects of IMT were only observed in studies with careful control of training intensity (i.e., training loads greater than 30% Pi, max) and patient selection. Patients with impaired inspiratory muscle strength and a ventilatory limitation to exercise with dyspnea as the main factor limiting exercise seem to have greater potential to benefit.

CONCLUSIONS

Strong evidence supports the use of exercise training to reduce symptoms, increase exercise capacity and improve quality of life in patients with COPD. Properly conducted exercise training has been shown to reduce ventilatory needs and DH during exercise at a given workrate. Several interventions might be useful adjuncts to exercise in primarily ventilatory-limited and hyperinflated patients who experience severe breathlessness during activities. Non-invasive ventilatory support and heliox breathing might be options for specialized centers. Oxygen supplementation and breathing exercises might be applied on a controlled trial and error basis, taking into account perceived benefits in terms of symptom reduction. Even though the evidence base for most breathing exercises (except for inspiratory muscle training) is small, the application of these techniques might

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be worthwhile (except for diaphragmatic breathing), since even modest benefits, when achieved with simple, non-invasive, and inexpensive interventions such as PLB, active expiration and body positioning, are of value to severely breathless patients. With all of these interventions, careful patient selection, proper and repeated instruction, control of techniques, and repeated assessments of perceived benefit in terms of symptom improvements are necessary. The transfer effects of controlled breathing exercises from resting to exercise conditions are not well established and further research should be performed in this area.

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C3.
Hyperinflation in the ICU

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Key Points

1.
The respiratory consequences of hyperinflation in spontaneously breathing, mechanically ventilated patients, are increased work of breathing, overdistention of the ventilatory pump (pump insufficiency), and wasted or ineffective efforts.

2.
The hemodynamic consequences of hyperinflation are decreased venous return, cardiac output and hypotension. These events are more pronounced in patients in intensive care units under mechanical ventilator support.

3.
The reduction of hyperinflation is the prime aim of the management of respiratory failure in intensive care units. However, this is not always feasible, since ventilator support modes may potentially increase overdistention of the respiratory system.

4.
Therapeutic approaches should include decreasing the level of extensive ventilator assistance by using the appropriate extrinsic PEEP and prolonging the time of expiration by reducing machine inspiratory timing (Ti) or by increasing the expiratory trigger threshold.

5.
Reducing wasted efforts of the patient is another complimentary therapeutic strategy.

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INTRODUCTION

The consequences of hyperinflation in spontaneously breathing mechanically ventilated patients are respiratory (*i.e.,* increased work of breathing, overdistention of the respiratory system and wasted or ineffective efforts) and hemodynamic compromise. In the passive patient (exhibiting no respiratory muscle activity) under controlled mechanical ventilation, the consequences of hyperinflation are overdistention and hemodynamic compromise.

Respiratory Consequences of Hyperinflation

The pathophysiology of hyperinflation of the respiratory system in spontaneously breathing mechanically ventilated patients can be illustrated using the Campbell diagram.

Campbell diagram

The Campbell diagram is constructed by plotting the dynamic relation between pleural pressure (measured with an esophageal balloon) and lung volume during breathing in relation to the passive pressure-volume curves of the lung $Pel_{(L)}$ and the chest wall $Pel_{(cw)}$ (**Figure 1**). The $Pel_{(cw)}$ is constructed by connecting the values taken by the esophageal pressure during passive inflation (*i.e.,* with no respiratory muscle activity) when the airways are closed at different lung volumes. Unfortunately, as this is difficult to do, since it requires passive inflation and often muscle paralysis, a theoretical value for the slope of this curve is frequently used. However, if a patient is passively ventilated and an esophageal balloon is placed, a true value for the volume–pressure relationship of the chest wall during passive tidal breathing can be obtained. This passive pressure–volume relationship can be used as a reference value for subsequent calculations when the patient develops spontaneous inspiratory efforts. Any change in esophageal pressure is referred to this line in the Campbell diagram in order to calculate the true muscular pressure developed by the patient. In normal subjects, inspiration starts from the relaxation volume of the respiratory system (V_r), where the $Pel_{(L)}$ and $Pel_{(cw)}$ intersect (*i.e.,* where the tendency of the lung to recoil inward is equal to the tendency of the chest wall to expand; **Figure 1**). Inspiratory muscle action results in pressure development (P_{insp}) on the left of the $Pel_{(cw)}$. Inspiratory flow,

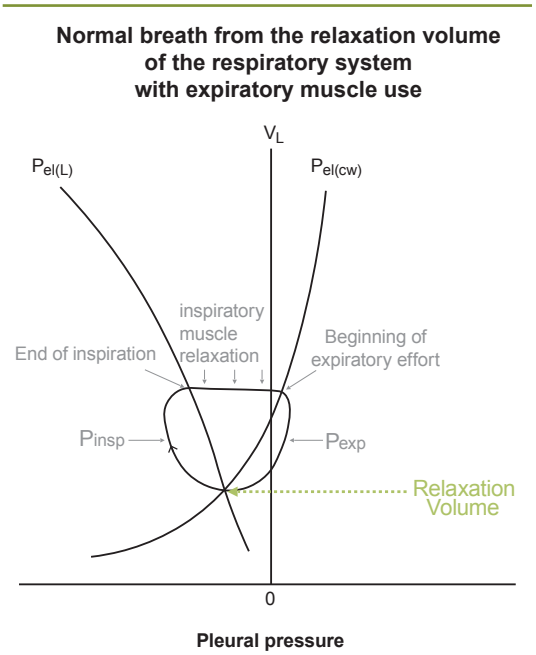

Figure 1. *In normal subjects, inspiration starts from the relaxation volume of the respiratory system, where the passive pressure-volume curves of the lung ($Pel_{(L)}$) and chest wall ($Pel_{(cw)}$) intersect. Inspiratory muscle action results in pressure development (P_{insp}) on the left of the pressure-volume curve of the chest wall ($Pel_{(cw)}$) . Inspiratory flow, and thus increases in lung volume (V_L) take place on the left of the pressure-volume curve of lung and coincide with the beginning of inspiratory muscle action. Inspiration ends on the pressure-volume curve of the lung and the inspiratory muscles relax (so that pressure returns on the pressure volume curve of the chest wall). In the case shown, expiration is active so that pressure develops on the right of the pressure volume curve of the chest wall due to activity of expiratory muscles (P_{exp}). This returns volume back to the relaxation volume of the respiratory system.*

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and thus increases in lung volume (V_L), take place on the left of the $Pel_{(L)}$ and coincide with the beginning of inspiratory muscle action. At any volume, the horizontal distance between the $Pel_{(cw)}$ and $Pel_{(L)}$ represents the portion of inspiratory muscle action devoted to expanding the lung at this volume with open airways (elastic pressure), and the portion on the left of the $Pel_{(L)}$ represents the pressure dissipated to generate airflow (resistive pressure). Inspiration ends on the $Pel_{(L)}$ (point of zero flow) and the inspiratory muscles relax so that pressure returns on the $Pel_{(cw)}$. Expiration is usually passive, and the respiratory system returns to its relaxation volume along the $Pel_{(cw)}$; however, in patients with respiratory distress, such as mechanically ventilated chronic obstructive pulmonary disease (COPD) patients, expiration is frequently active. In the case of active expiration, pressure develops on the right of the $Pel_{(cw)}$ due to activity of expiratory muscles (P_{exp}). This returns volume back towards the relaxation volume of the respiratory system.

In mechanically ventilated patients, inspiratory muscle action has to overcome the trigger sensitivity (P_{tr}) of the ventilator (horizontal distance between the $Pel_{(L)}$ curve and P_{tr}; **Figure 2**) before it results in inspiratory flow and thus increases in V_L. Thus, the beginning of inspiratory effort does not coincide with the beginning of inspiratory flow. Instead, the initial inspiratory effort (orange line in **Figure 2**) is horizontal (no flow, only pressure development) until it crosses the P_{tr} line at which time it deviates upward, indicating inspiratory flow, and thus increases in V_L.

Work of breathing

Measuring work of breathing (WOB) is a useful approach to calculate the total expenditure of energy by the respiratory muscles and/or the ventilator. In general, the work performed during each respiratory cycle is mathematically expressed as $WOB = \int Pressure \times Volume$, *i.e.,* the area on a pressure–volume diagram (**Figure 1-2**). Esophageal pressure is usually taken as a surrogate for intrathoracic (pleural) pressure. Esophageal pressure swings during inspiration are needed to overcome two forces: the elastic forces of the lung parenchyma and chest wall, and the resistive forces generated by the movement of gas through the airways. One can calculate these two components (elastic and resistive) by comparing the difference between esophageal pressure during the patient's effort during the breath and the pressure value in passive

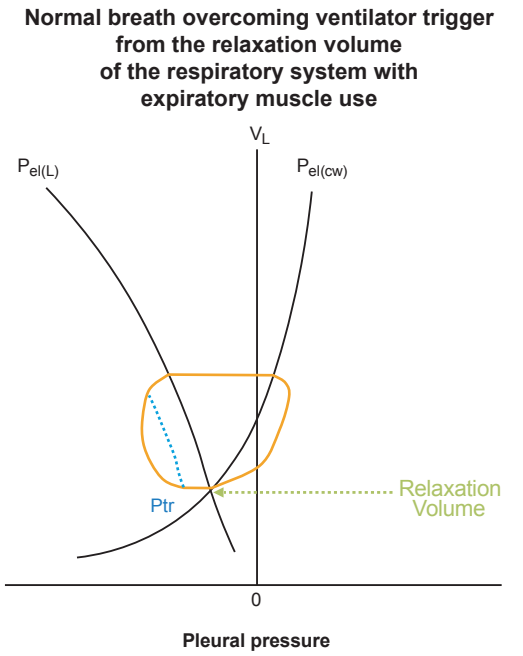

Figure 2. *In mechanically ventilated patients, inspiratory muscle action has to overcome the trigger sensitivity of the ventilator (horizontal distance between the $Pel_{(L)}$ curve and P_{tr}) before it results in inspiratory flow and thus increases in V_L. Thus, the beginning of inspiratory effort does not coincide with the beginning of inspiratory flow. Instead, the initial inspiratory effort (orange line) is horizontal (no flow, only pressure development) until it crosses the P_{tr} line at which time it deviates upward indicating inspiratory flow and thus increases in V_L. In the case shown, the trigger sensitivity is pressure triggering.*

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conditions, represented by the static $Pel_{(cw)}$. The area between the $Pel_{(L)}$ and $Pel_{(cw)}$ represents the elastic work of breathing. The area on the left of the $Pel_{(L)}$ represents the resistive work of breathing. The area on the right of the $Pel_{(cw)}$ represents the work of breathing of the expiratory muscles.

The WOB is normally expressed in joules (J). One J is the energy needed to move 1L of gas through a 10-cmH_2O pressure gradient. The work per liter of ventilation (J/L) is the work per cycle divided by the tidal volume (expressed in liters). In a healthy subject the normal value is around 0.35 J/L. Lastly, WOB can be expressed in *work per unit of time*, multiplying joules per cycle by the respiratory rate (expressed in breaths per minute) to obtain the power of breathing (joules/minute). In a healthy subject the normal value is around 2.4 J/min.

As illustrated by the Campbell diagram, hyperinflation increases the WOB: the higher the End-expiratory lung volume (EELV), *i.e.*, the higher the intrinsic positive end-expiratory pressure (PEEPi), the larger the area of the work of breathing on the Campbell diagram. This is because the $Pel_{(L)}$ and $Pel_{(cw)}$ both deviate as lung volume increases. Consequently, with a constant tidal volume (V_T), the higher the EELV, the larger the elastic component of the work of breathing, and thus the total work of breathing. Intrinsic positive end-expiratory pressure can be quite high, especially in patients with COPD, and may represent a high proportion of the total WOB. For example, a patient who displaces 0.5L of tidal volume through a 7-cmH_2O pressure gradient will perform an amount of work of 0.35J/cycle. If nothing else changes except that this patient develops 5 cmH_2O of PEEPi, 0.25J will be required to counterbalance this, meaning that the total WOB will be 0.60J (0.35 + 0.25), which represents around 40% of the total work required for the inspiration.

Overdistention

In patients with hyperinflation, inspiration starts from an increased EELV, which predisposes to overdistention. The higher the hyperinflation and the higher the inspiratory pressure or volume delivered by the ventilator, the higher the risk of overdistention. The presence of overdistention can be inferred from the airway pressure over time tracing of the ventilator screens when late inspiratory upstroke develops (**Figure 3**).

Wasted efforts

Wasted or ineffective efforts are inspiratory efforts that fail to trigger the ventilator. Nearly 25% of mechanically ventilated patients exhibit ineffective efforts, which are even more frequent in COPD patients. Wasted efforts are a major cause of patient-ventilator dyssynchrony that increase the energy expenditure of the respiratory muscles and may injure them. Understanding their pathophysiology is essential to properly adjust the ventilator settings to attenuate or eliminate them. Wasted efforts should be searched for before any change in ventilator settings is implemented during assisted modes of mechanical ventilation, since any ensuing (after the change in ventilator settings) increase in ventilator rate might be caused by the attenuation of wasted efforts (the ventilator rate now approaching the patient's respiratory controller rate) and not by the development of respiratory distress with the new settings.

How can wasted efforts be detected at the bedside?

Wasted efforts can be clinically detected when the breaths delivered by the ventilator (measured rate on the ventilator display) are less than the number of inspiratory efforts of the patient (on clinical examination) over the same time interval. On modern ventilator screens, ineffective efforts can be detected as

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Effects of PEEP on wasted efforts in the presence of dynamic hyperinflation and PEEPi.

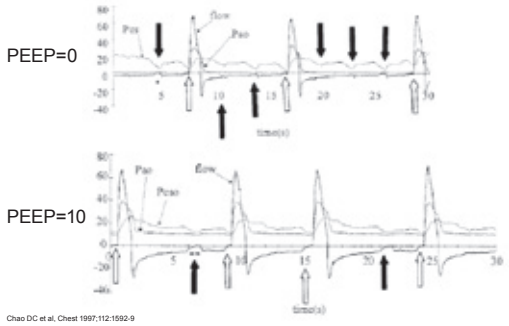

Figure 3. *Upper panel: Esopageal (P_{eso}) and airway (P_{ao}) pressures and flow at the tracheostomy in a patient with wasted efforts (black arrows) on flow-controlled, volume-cycled (assist/control) mode. Wasted efforts can be detected as abrupt airway pressure drop simultaneous to an abrupt decrease in expiratory flow (from the flow trajectory established earlier during expiration) caused by the inspiratory effort and not followed by a machine breath. The units are cm H_20 for the pressure tracing and L/min for flow. The patient's inspiratory efforts are identified by the negative P_{eso} swings. The PEEP is set at 0. Pao appropriately drops to 0 during expiration; demonstrating little circuit or valve resistance. Wasted efforts (black arrows) are evident, with one triggered breath (white arrow) every two to three inspiratory efforts. Prolonged expiratory flow is due to airflow limitation. Lower panel: PEEP is now increased to 10 cm H_20 so the P_{ao} during expiration is now 10 cm H_20. There is persistent flow at end-expiration, thus PEEPi is still present. Wasted efforts (black arrows) have been reduced with one breath triggered every other inspiratory effort. Peak inspiratory pressure and the P_{eso} have increased slightly compared to the upper panel, most likely indicating a higher end-expiratory lung volume and total PEEP level.*

abrupt airway pressure drops simultaneous to an abrupt decrease in expiratory flow (from the flow trajectory established earlier during expiration) caused by the inspiratory effort, and not followed by a machine breath (**Figure 3**). Monitors that can automatically detect wasted efforts are available.

Why are spontaneously breathing mechanically ventilated COPD patients prone to develop wasted/ineffective efforts?

In COPD patients with hyperinflation, inspiration starts from an increased end-expiratory lung volume (**Figure 4**). Inspiratory muscle action has to overcome the PEEPi (red dashed line, horizontal distance between the $Pel_{(L)}$ and $Pel_{(cw)}$) before it results in inspiratory flow and thus increases in V_L. In mechanically ventilated patients, inspiratory muscle action has to additionally overcome the Ptr of the

Breath from increased end-expiratory lung volume due to the presence of dynamic hyperinflation in COPD

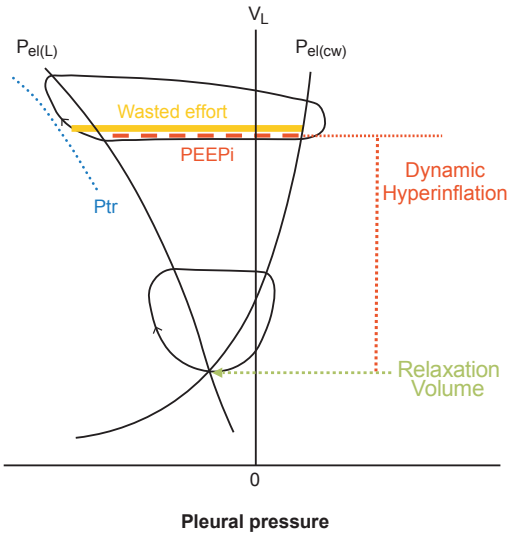

Figure 4. *In COPD patients with dynamic hyperinflation, inspiration starts from an increased end-expiratory lung volume. Inspiratory muscle action has to overcome the intrinsic positive end expiratory pressure (PEEPi, horizontal distance between the between the $Pel_{(L)}$ and $Pel_{(cw)}$) before it results in inspiratory flow and thus increases in volume. In mechanically ventilated patients, inspiratory muscle action has to overcome PEEPi plus the trigger sensitivity (P_{tr}) before it results in inspiratory flow and thus increases in volume (V_L). When the magnitude of inspiratory muscle action is less than the sum of PEEPi + P_{tr}, this inspiratory effort (orange horizontal line) cannot trigger the ventilator, and consequently does not result in inspiratory flow and thus increases in volume (V_L). This inspiratory effort is called ineffective or wasted.*

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ventilator (horizontal distance between the $Pel_{(L)}$ and P_{tr}) before it results in inspiratory flow and thus increases in V_L; thus, in mechanically ventilated COPD patients, inspiratory muscle action has to overcome PEEPi plus the P_{tr}. When the magnitude of inspiratory muscle action is less than the sum of PEEPi plus P_{tr}, this inspiratory effort (**Figure 4**, orange line) cannot trigger the ventilator, and consequently does not result in inspiratory flow and thus increases in V_L. This inspiratory effort is called "ineffective" or "wasted".

Hyperinflation not only increases PEEPi, but at the same time renders the respiratory muscles weaker for a variety of reasons: (see chapter A1).

The greater the degree of hyperinflation, the higher the PEEPi, and the weaker become the respiratory muscles. The net effect is a greater predisposition to wasted efforts.

Is the Campbell diagram useful for estimating the work of breathing during wasted efforts?

The Campbell diagram is not useful to estimate inspiratory work of breathing when inspiratory triggering does not happen (*i.e.,* during wasted efforts): work is physically defined as the area subtended in a pressure/volume loop. Since there is no inspiratory volume, the work is zero (albeit muscles, indeed, consume energy). The energy expenditure during non-triggered wasted inspiratory efforts can be estimated by the pressure/time product: the product of the pressure developed by the inspiratory muscles (difference between the measured esophageal pressure and the $Pel_{(cw)}$) multiplied by the time of muscle contraction (*i.e.,* neural inspiratory time [Ti]).

How are ventilator settings affecting the incidence of wasted/ineffective efforts?

Excessive ventilator support predisposes to ineffective efforts irrespective of the mode of mechanical ventilation used. This is because, in the case of COPD, excessive pressure or volume delivered by the ventilator results in increased EELV, and this combined with the long time constant of the respiratory system (which retards lung emptying) and/or a short imposed expiratory time (in case of volume or pressure control) results in further increased EELV before the next inspiratory effort begins (**Figure 5**, green curve).

At the same time, excessive ventilator assistance reduces inspiratory muscle effort, via either a phenomenon called neuromechanical inhibition (the main mechanism most likely being the Hering–Breuer reflex), and/or by producing alkalemia via excessive CO_2 reduction in patients with chronic bicarbonate elevation, thus reducing the drive to the respiratory muscles.

The ensuing inspiratory effort is inadequate to overcome PEEPi plus Ptr; thus, this inspiratory effort fails to trigger the ventilator (ineffective or wasted effort) (**Figure 5**, red line). This is, of course, exaggerated in the presence of respiratory muscle weakness. The next expiratory effort (**Figure 5**, blue curve) decreases the EELV. When EELV decreases to a level where the ensuing inspiratory effort exceeds PEEPi plus Ptr, the ventilator is triggered again to deliver a machine breath (**Figure 5**, purple curve). The breath-to-breath variability in breathing pattern contributes to the variability in the EELV and thus to the frequency of ineffective efforts.

During assist volume or pressure control mechanical ventilation, prolonged imposed inspiratory time (machine Ti) greater than the patient's neural Ti results in a situation where the ventilator is inflating the patient long after the inspiratory muscles have stopped their

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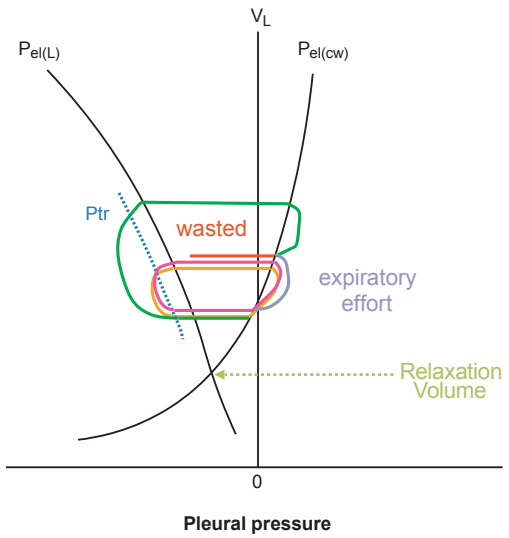

Figure 5. *In the case of COPD presented in this figure, the first inspiratory effort (orange line) triggers the ventilator. In the next breath that triggered the ventilator, excessive ventilator assistance (either pressure or volume) resulting in large tidal volume, combined with the long time constant of the respiratory system (which retards lung emptying) and/or a short imposed expiratory time (in case of volume or pressure control) result in further increased end-expiratory lung volume before the next inspiratory effort begins (green line). The ensuing inspiratory effort despite being equal to the previous effective effort is inadequate to overcome PEEPi + P_{tr} due to the increased EELV. Thus this inspiratory effort fails to trigger the ventilator (wasted or ineffective effort, red line). The following expiratory effort (blue line) decreases the end-expiratory lung volume. When the end-expiratory lung volume decreases to a level where the ensuing inspiratory effort exceeds PEEPi +P_{tr}, the ventilator is triggered again to deliver a machine breath (purple line).*

contraction, *i.e.*, during the neural expiration. This results in increased EELV and a shorter time available for expiration, both of which increase EELV (more hyperinflation) and thus predispose to wasted efforts.

During pressure support ventilation, a low expiratory trigger threshold (percentage of peak inspiratory flow at which the ventilator cycles to expiration) might lead to pressure support being delivered well beyond the patient's neural Ti. The next inspiratory effort (controlled by the patient's respiratory controller) begins during the early phase of ventilator expiration, *i.e.*, at an increased VL. This effort might not be sufficient to overcome PEEPi plus Ptr, and thus, this inspiratory effort also fails to trigger the ventilator.

Therapeutic approach to overdistention

An obvious solution to reduce overdistention is to decrease the level of excessive ventilator assistance (*i.e.*, the delivered pressure or volume). This will decrease EELV. However, this might not be always clinically feasible, since it might lead to respiratory distress and derangement of blood gases.

Another not mutually exclusive approach is to decrease hyperinflation by prolonging the expiratory time. With a constant VT, decreasing hyperinflation will decrease overdistention:

1. During assist volume or pressure control, reducing machine Ti (or equivalently increasing the inspiratory flow in volume control) may prolong expiratory time (if the respiratory frequency, and thus the total time of the respiratory cycle, does not change) and will reduce hyperinflation.
2. During pressure support, increasing the expiratory trigger threshold will stop the breath earlier, *i.e.*, at a lower EELV, and will prolong expiratory time and thus, will decrease hyperinflation.

Therapeutic approach to wasted efforts: What ventilator adjustments should be done in the presence of wasted/ineffective efforts?

One solution to reduce the frequency of wasted efforts is to decrease the level of excessive ventilator assistance (*i.e.*, the delivered pressure or volume). This will decrease the EELV and with a given (or even

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increased) time for expiration will reduce EELV-hyperinflation and will reverse the pathophysiology presented above. In clinical practice one may start gradually decreasing the level of applied pressure during assist pressure control or pressure support in steps of 2 cm H_2O or the delivered volume in assist volume control by 10%. However, this might not be always clinically feasible, since it might lead to respiratory distress and to derangement of blood gases.

During assist volume or pressure control reducing machine Ti (or equivalently increasing the inspiratory flow in volume control) may prevent ventilator delivery beyond the patients' neural Ti. This will prolong expiratory time and will reduce wasted efforts. In practice, machine Ti may be reduced in steps of 10%. This titration may be stopped when ineffective triggering is eliminated or the patient shows poor tolerance. During pressure support, increasing the expiratory trigger threshold will stop the breath earlier, and thus at a lower EELV, and will prolong expiratory time. Both will reduce wasted efforts. Practically, the insufflation time may be gradually reduced, by increasing the cycling-off criterion in steps of 10%; if ineffective triggering persists at the highest value (which depends on the ventilator), the insufflation time may be further reduced by adjusting the maximal insufflation time in steps of 0.2s from the mean insufflation time; this titration may be stopped when ineffective triggering is eliminated or the patient shows poor tolerance.

Another solution is the application of PEEP. The addition of an amount of external PEEP lower than the PEEPi (**Figure 6**, red dotted lines) offers part of the pressure required to overcome PEEPi plus P_{tr} (**Figure 6**). The inspiratory effort starts closer to the $Pel_{(L)}$ (the horizontal distance between this point and the Pel(cw) being the applied PEEP [PEEP external]). The inspiratory effort is now adequate to trigger the ventilator (orange curve).

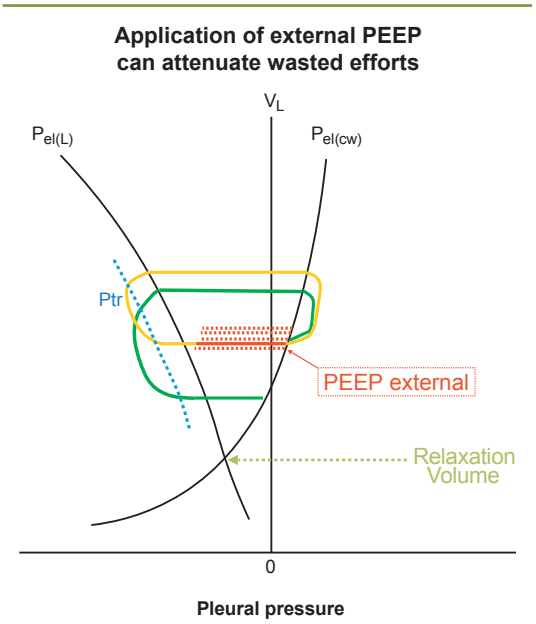

Figure 6. *In the presence of increased EELV (green line), addition of an amount of external PEEP lower than the PEEPi (red dotted lines) offers part of the pressure required to overcome PEEPi+P_{tr}. The inspiratory effort starts closer to the passive pressure-volume curve of the lung ($Pel_{(L)}$). The horizontal distance between this point and the passive pressure- volume curve of the chest wall ($Pel_{(cw)}$) is the applied PEEP (PEEP external). The inspiratory effort is now adequate to trigger the ventilator (orange line).*

In clinical practice, one may begin by applying small amounts of PEEP (e.g., 2 cmH_2O) and gradually increase the applied PEEP until wasted efforts obtain their minimal value. Increasing the applied PEEP above a certain value, i.e. the value of PEEPi (which is, however, difficult to measure), will increase the end inspiratory lung volume and will start to predispose again to wasted efforts. The greater the increase of applied PEEP above PEEPi, the more likely the reappearance or increase in the number of wasted efforts.

Measurement of PEEPi

It becomes obvious that an accurate measurement of PEEPi is needed. In passive

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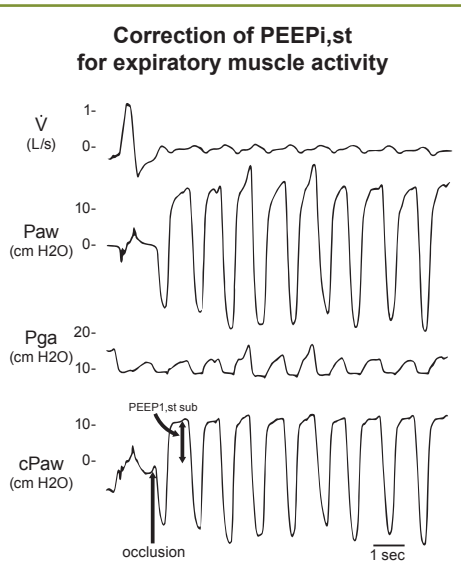

Figure 7. *Recordings of Flow ($\dot{V}$), P_{aw}, P_{ga}, and on line "corrected" airway pressure (cP_{aw}) in a representative actively expiring patient during airway occlusion. cP_{aw} is obtained by subtracting the P_{ga} exp rise from P_{aw}. Note a consistent end-expiratory plateau in cP_{aw}, despite marked variability in P_{ga} swings. From this plateau, the PEEPi,st sub is measured.*

mechanically ventilated patients, PEEPi is routinely measured under static conditions (PEEPi,st, or static PEEPi) as the plateau in airway pressure during a prolonged end-expiratory airway occlusion. In spontaneously breathing mechanically ventilated patients estimation of PEEPi is difficult without the placement of esophageal balloons and gastric balloons. In actively breathing patients on assisted ventilation, PEEPi has been assessed dynamically from records of esophageal pressure (Pes) obtained with the placement of an esophageal balloon. The decrease in Pes needed to abruptly bring expiratory flow to zero during unoccluded breathing is taken as dynamic PEEPi (PEEPi,dyn).

However, expiratory muscle activity (which causes an expiratory rise in gastric pressure measured with a gastric balloon [Pga,exp rise]) can increase the end-expiratory alveolar pressure independently of dynamic hyperinflation, leading to an overestimation of PEEPi. In spontaneously breathing and actively expiring patients, PEEPi,st can be corrected for expiratory muscle contraction by synchronously subtracting the expiratory rise in gastric pressure (Pga,exp rise) from the end-expiratory airway pressure (Paw) occurring during airway occlusion (**Figure 7**, PEEPi,st sub).

In the case that PEEPi,dyn is part of the decrease in Pes preceding inspiration, which

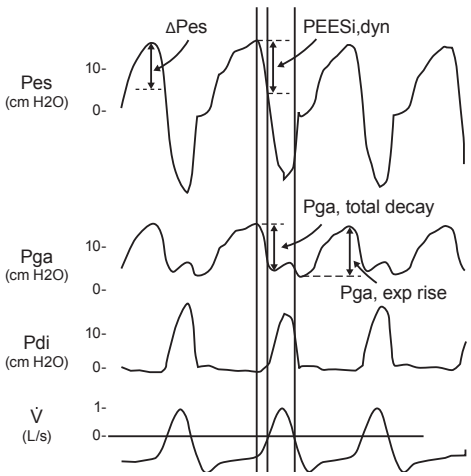

Figure 8. *Tracings of esophageal pressure (P_{es}), gastric pressure (P_{ga}), transdiaphragmatic pressure (Pdi) and flow ($\dot{V}$) in a patient actively expiring during a spontaneous breathing trial through the ventilator (pressure support of 6 cm H_2O). The three vertical lines are passed through the onset of inspiratory muscle activity (i.e., beginning of P_{es} decay) and the beginning and the end of inspiratory flow, respectively. Note the large increase of P_{ga} and P_{es} during expiration due to expiratory muscle recruitment. ΔP_{es} is the increase in end-expiratory P_{es} relative to its level at the onset of spontaneous breathing trial, when expiratory muscle activity was nil. P_{ga}, total decay represents the abrupt decrease in Pga from its maximum end-expiratory value to its minimum value at the beginning of inspiration due to relaxation of the abdominal muscles. P_{ga}, exp rise is the P_{ga} rise from its minimal end-inspiratory level to the maximal level at end expiration. The decay in P_{es} between the first two vertical lines represents dynamic intrinsic positive end-expiratory pressure (PEEPi,dyn).*

is measured as PEEPi,dyn, is actually due to relaxation of the expiratory muscles, rather than contraction of the inspiratory muscles to counterbalance PEEPi. The amount of pressure due to expiratory muscle activity that should be subtracted from the measured PEEPi,dyn to obtain the actual ("true") PEEPi,dyn elicited by dynamic hyperinflation is either the increase in gastric pressure over the course of expiration (Pga,exp rise) attributed to expiratory muscle contraction or the total decrease in gastric pressure observed at the beginning of inspiration attributed to expiratory muscle relaxation (Pga,total decay); the latter being somewhat more accurate than the former (**Figure 8**).

HEMODYNAMIC CONSEQUENCES OF HYPERINFLATION

At the end of a normal expiration, alveolar and airway pressures are zero relative to atmosphere, and esophageal pressure is negative (around -5 cmH_2O in normal conditions). However, in the presence of hyperinflation (because of either dynamic airway collapse or inadequate time to exhale), the alveolar pressure remains positive throughout expiration. This positive alveolar pressure is transmitted to the pleural-intrathoracic cavity to varying degrees depending on the compliance of the lung. In the case of COPD patients, the lungs are compliant, so most of the positive alveolar pressure is transmitted to the intrathoracic cavity. This increases the mean intrathoracic pressure during the whole respiratory cycle. The effect is more pronounced in the passive patient, because during inspiration (pressure or flow delivery by the ventilator), the intrathoracic pressure becomes even more positive than the pressure existing at the end of expiration. In the spontaneously breathing mechanically ventilated patient, the inspiratory effort of the patient decreases the mean inspiratory pressure and thus the mean intrathoracic pressure. However the average, *i.e.,* the mean intrathoracic pressure, is still positive. The more positive the mean intrathoracic pressure, the more pronounced its hemodynamic effects. The hemodynamic effects of hyperinflation are the result of a complex interaction between changes in preload, secondary to changes in the venous return, right—left ventricle interactions, direct effects of lung inflation and changes in afterload. At moderate degrees of hyperinflation, decreased venous return is the main mechanism leading to decreased cardiac output. The hyperinflated lung compresses the pericardium and especially the pericardial fossa, increasing their pressure (pericardial and juxtacardial respectively). This pressure is transmitted to the right atrial cavity increasing the right atrial pressure, which is the downstream pressure for venous return. However, hyperinflation with the resulting PEEPi also elevates the upstream pressure driving venous return (*i.e.,* the mean systemic pressure) by both reflex and mechanical means, independent of the abdominal pressure. The positive intrathoracic pressure also changes the resistive and elastic properties of peripheral veins, increases venous resistance, and directly compresses the inferior vena cava. The net effect of all these phenomena is a decrease in the venous return.

At the same time that hyperinflation decreases the preload of the right ventricle, it also increases its afterload, *i.e.,* the pulmonary vascular resistance. The more lung volume increases above the relaxation volume of the respiratory system, the more the intra-alveolar vessels are compressed, creating a starling resistor phenomenon. This dominates over vessel recruitment, resulting in increased pulmonary vascular resistance. The combination of decreased preload and increased afterload of the right ventricle

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results in decreased stroke volume, and thus in decreased preload of the left ventricle. Despite the fact that the elevations in intrathoracic pressure decrease the transmural pressures of the left heart, and thus its afterload, the net effect is a decrease in cardiac output and/or hypotension.

Of course, the effects of hyperinflation on hemodynamics also depend on the contractile function of the right and left heart and the volume status of the patient. The more hypovolemic (volume depleted) a patient is, the more vulnerable they become to the effects of hyperinflation on the venous return and the right ventricular afterload; thus, the more vulnerable the patient to the development of hypotension and decreased cardiac output.

In spontaneously breathing mechanically ventilated patients, application of external PEEP is beneficial to counterbalance intrinsic PEEP (see above). The hemodynamic effects of this PEEP application depend on its magnitude. Positive end-expiratory pressure amounting to 85-90% of PEEPi have no hemodynamic effects, whereas levels of PEEP above this level and especially well above PEEPi (e.g., by 5cmH_2O) decrease cardiac output. It is needless to say that levels of PEEP that are higher than PEEPi are counterintuitive, and should not be used.

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C4. Surgical Approaches for Lung Volume Reduction

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Key Points

1.
Surgical approaches for lung hyperinflation remain largely underused in practice.

2.
The key for a successful surgery is careful patient selection where the benefits clearly exceed the risks.

3.
As a rule of thumb, a chronic obstructive pulmonary disease patient should only be considered for a surgical approach when dyspnea remains a limiting symptom, despite optimal pharmacological therapy and effective pulmonary rehabilitation.

4.
The ideal candidate for bullectomy is a chronic obstructive pulmonary disease patient with a FEV_1 < 50% pred. showing a large bullae (greater than one-third of the hemithorax) compressing a relatively normal lung.
The ideal candidate for lung volume reduction surgery is a chronic obstructive pulmonary disease patient with emphysema predominance showing heterogeneous disease with upper lobe predominant disease and poor exercise capacity.

5.
Despite potential subjective and functional improvements in well-selected candidates, the beneficial consequences of any surgical approach tend to deteriorate over time.

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INTRODUCTION

There is long-standing interest in establishing effective and lasting surgical alternatives to reduce lung volumes in patients with emphysema. These approaches make sense, as emphysema is, by definition, a destructive and non-reversible process. In fact, the efficacy of medical/pharmacological options in deflating the lungs is limited when the main mechanism of lung hyperinflation is no longer expiratory flow limitation, but the anatomical consequences of alveolar destruction per se. As expected, the main challenge facing the physician is to balance the potential benefits against the risks of offering surgery to severely disabled patients in which chronic obstructive pulmonary disease (COPD) frequently coexists with several morbidities. This chapter will provide an up-to-date guide on how to reach the best decision on whether a patient may or may not benefit from a surgical procedure aimed at deflating the lung(s). Although several surgical procedures have been proposed in the past 80 years, only the few which have survived the test of time will be discussed herein.

Bullectomy

Definitions

Lung bullae are air-filled spaces exceeding 1cm in diameter with a wall thickness less than 1mm. The outer surface of a typical bulla is made of visceral pleura, but the inner surface consists of fibrous tissue formed by the pleura and underlying destroyed pulmonary parenchyma. A bulla which becomes substantially enlarged and occupies a large volume (at least one-third) of the chest cavity is called a "giant bulla". Giant bullous emphysema (vanishing lung syndrome) is an idiopathic and distinct clinical syndrome that affects young men, usually smokers (including marijuana), and is characterized by extensive, predominantly asymmetric upper lobe bullous emphysema. The following classification of bullae is useful to guide treatment options:

Group I: Single large bulla with underlying normal/relatively-normal lung;

Group II: Multiple bullae with underlying normal normal/relatively-normal lung;

Group III: Multiple bullae with underlying diffusely emphysematous lung;

Group IV: Multiple bullae with underlying lung affected by other diseases.

Procedures

Bullectomy (also known as reduction pneumoplasty) is a thoracic surgery procedure aimed at excising one or more lung bullae. The bullae can be resected via an "open" technique; usually a thoracotomy (staged or simultaneous bilateral) or sternotomy. Alternatively, a video-assisted thoracoscopic surgery (VATS) approach may be feasible in selected cases. If the bulla has destroyed or replaced much of the lung parenchyma, then an anatomical resection (segmentectomy or lobectomy) may be required. Giant bullectomies can also be concomitantly done with lung volume reduction surgery (LVRS) on the ipsilateral and contralateral lung. An alternative approach for frail patients with a large single bullae is the Monaldi procedure (Brompton technique), in which the bulla is drained percutaneously and a catheter is left behind. The catheter is put under suction for a few days, after which the broncho-cutaneous fistula closes spontaneously after removal.

How does bullectomy work?

It is widely believed that bullae form when adjacent areas of paraseptal emphysema coalesce, which explains why they are usually subpleural in distribution. The right upper lobe is

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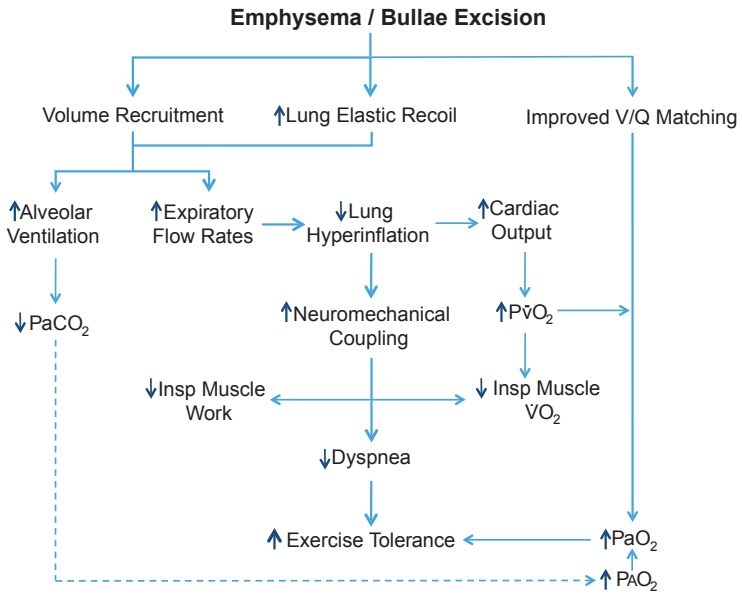

Figure 1. Potential physiological and sensory benefits of surgical volume reduction contributing to increase exercise tolerance in patients with COPD. Key mechanisms are highlighted in bold and thicker connectors. See text for elaboration. insp: inspiratory; V: ventilation; Q: perfusion; VO_2: oxygen uptake; PaO_2: arterial partial pressure for oxygen; $PaCO_2$: arterial partial pressure for carbon dioxide. PAO_2, alveolar partial pressure for oxygen.

disproportionately affected, probably because alveoli from this lobe are characteristically over-distended compared to those from other lobes. Although small bullae may increase due to a "ball-valve mechanism" in which gas enters the lesion but cannot escape, larger bullae have negative intra-bullous pressure (i.e., similar to pleural pressure). This explains why they are preferentially ventilated during inspiration. Air trapping ensues because there is little inward recoil, forcing the air to leave the bulla. The final consequence is compression of lung tissue immediately adjacent to a bulla. As detailed in the preceding chapters, the resulting hyperinflation of the chest interferes with normal respiratory mechanics, increasing the work of breathing with associated exercise limitation and dyspnea.

The physiological changes underlying the benefits of bullectomy are quite similar to those described after LVRS (**Figure 1**). First and foremost, there is a significant reduction in total lung capacity (TLC) and functional residual capacity (FRC); consequently, tidal volume (V_T) becomes positioned on a more compliant portion of the pressure-volume relation of the respiratory system. The inspiratory muscles may derive large mechanical benefits due to: 1) diaphragmatic lengthening and partial reconfiguration of its normal curvature; 2) improved length-tension relationship; 3) partial restoration of the zone of apposition with more effective coupling of the costal diaphragm and the lower intercostal muscles; and 4) reduced elastic loading. Improvement in expiratory flow rates after bullectomy is likely secondary to recruitment of functioning airways because forced expiratory volume in one second (FEV_1) usually increases in tandem with forced vital capacity (FVC), i.e., FEV_1/FVC does not change remarkably. Tidal expiratory flow limitation, however, may persist, albeit at lower lung volumes (**Figure 2**). On the other hand, if the excised bullae are not communicating with the larger airways, little effect is expected on absolute dead space (V_D). More importantly, however, V_D relative to V_T may decrease as a result of volume recruitment secondary to bullous deflation. The ultimate consequence may be lower ventilatory requirement to meet a given metabolic demand, as a small fraction of V_T is "wasted". Additional potential effects of

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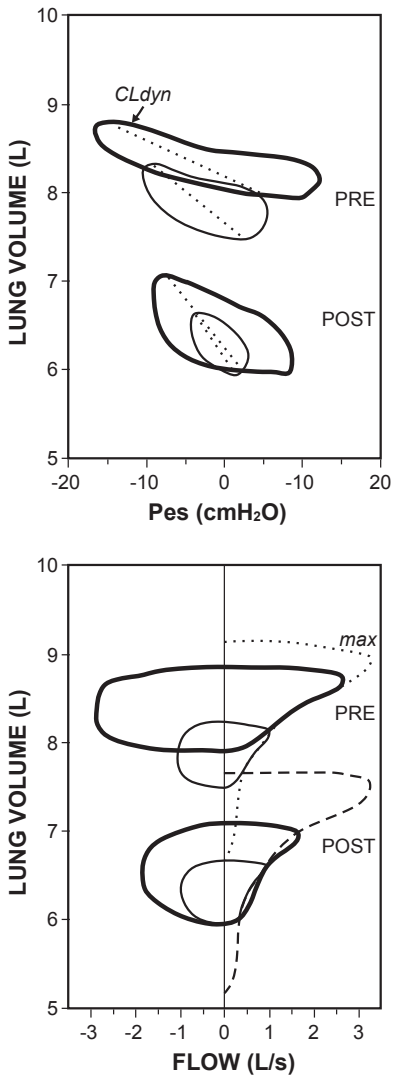

Figure 2. *Changes in lung volume as a function of changes in pleural pressure (represented by esophageal pressure (P_{es})) (upper panel) and flow (lower panel) at rest (thin lines) and exercise (thick lines) in a patient with advanced emphysema who underwent bullectomy and LVRS. Note that after surgery ("post"): a) lower variations in Pes were required to elicit greater changes in volume, i.e., dynamic compliance (CLdyn) improved and b) tidal expiratory flow limitation persisted, albeit at lower lung volumes.*

Adapted from: O'Donnell DE, Webb KA, Bertley JC, Chau LK, Conlan AA. Mechanisms of relief of exertional breathlessness following unilateral bullectomy and lung volume reduction surgery in emphysema. Chest. 1996;110(1):18-27.

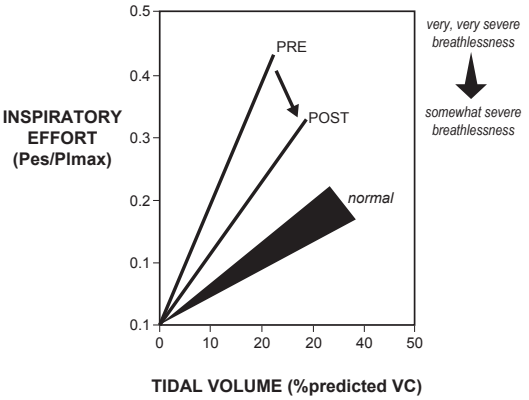

Figure 3. *Lung deflation post-bullectomy results in a more harmonious relationship between inspiratory effort (ratio between esophageal and maximal inspiratory pressures (P_{es}/P_{Imax}) and chest wall displacement). The improvement in neuro-mechanical dissociation is centrally interpreted as a relief of respiratory difficulty ("shortness of breath").*

Adapted from: O'Donnell DE, Webb KA, Bertley JC, Chau LK, Conlan AA. Mechanisms of relief of exertional breathlessness following unilateral bullectomy and lung volume reduction surgery in emphysema.Chest. 1996;110(1):18-27.

bullectomy on pulmonary gas exchange and central hemodynamics are discussed below

Several mechanisms may explain why bullectomy may improve exertional breathlessness (**Figure 3**), including reductions in impedance to inspiratory muscle action, functional inspiratory muscle weakness and ventilatory demand. In fact, one study found that 99% of improvement in exertional breathlessness at a standardized work rate was explained by the combination of decreased operating lung volumes, decreased breathing frequency, and reduced mechanical constraints on V_T, i.e., direct or indirect consequences of less hyperinflation. In summary, the main aim of bullectomy is to improve patients' dyspnea and respiratory-related quality of life by:

- promoting expansion of compressed normal adjacent lung tissue, thereby recruiting additional lung parenchyma for gas exchange and blood perfusion;

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- improving ventilatory mechanics and work of breathing.

Who are the best candidates for bullectomy?

Patients should only be considered for bullectomy if they report chronic dyspnea and poor respiratory-related quality of life, despite maximal medical treatment. Bullectomy can also be indicated for bullae-related complications, including infection, bleeding or carcinoma. There is a widespread notion that total resection of the bullae is of importance due to increased risk of development of bronchogenic carcinoma. Group I and Group II patients of bulle classification are considered the best candidates (**Table 1**). The size of the bulla also matters: best functional results are obtained when it is greater than 1/3 of the hemithorax. An estimate of the bulla size can also be obtained by comparing TLC by body plethysmography with that obtained by inhalation of a dilution gas (such as helium): the amount by which the second method underestimates TLC equals the bulla volume. There are also radiological techniques to estimate the volume of a bulla. Excision of bulla with volumes greater than 20% of the body plethysmographic-determined TLC usually results in functional improvement. Data from several case series and uncontrolled observational studies suggest that a significant and sustained functional and symptomatic improvement (up to 5 years) can be achieved in most (60-90%) of carefully selected patients.

Acute interventions due to rapidly progressing dyspnea, pneumothorax and/or prolonged air leak after chest tube insertion, are associated with greater risk. Surgery is usually contraindicated in patients who continue to smoke, have significant comorbidities (pulmonary hypertension, corpulmonale), present with hypercapnia and are aged 80 or over (**Table 1**). Hypoxemia *per se* is not a contraindication; as PaO_2 may increase after lung decompression. The most common complications are: air leaks (up to 50%), a residual intrathoracic pleural space, atrial fibrillation, pulmonary embolism, pneumonia and respiratory failure requiring mechanical ventilation. The surgery carries a mortality of up to 7% in most published series.

Positive features
• Bullae occupying more than one-third of the hemithorax
• Vascular crowding
• Localized disease
• Compression of underlying normal lung
• Relatively good perfusion on the contralateral side
• Preoperative FEV_1<50% pred.
Negative features / contraindications
• Extensive, diffuse emphysema
• Several small bullae
• Current smoking
• Significant cardiopulmonary comorbidities
• Age > 80 years
• Chronic hypercapnia

Table 1. *Clinical, imaging and functional characteristics of patients more likely to benefit from bullectomy and predictors of failure or complications.*

How to evaluate potential candidates for bullectomy

High resolution computerized tomography (HRCT) is the imaging technique of choice to determine the extent and distribution of bullous disease. High resolution computerized tomography also allows assessment of coexisting problems such as bronchiectasis, co-infected cysts, pulmonary artery enlargement and pneumothorax. The basic evaluation includes

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electrocardiogram, echocardiogram, dyspnea quantification (at least the Medical Research Council graduation), full pulmonary function tests (including arterial blood gases and body plethysmography) and a measure of functional exercise capacity (at least the 6-minute walking test). As mentioned, comparison of TLC measured by body plethysmography and any technique based on dilution of an inert gas may prove useful to pre-operatively estimate bullae volume.

Lung volume reduction surgery (LVRS)

Definitions

The term "lung volume reduction surgery" (LVRS) defines a surgical procedure aimed at deflating the lung by excising the most affected portions of the organ in patients with a predominant emphysema phenotype.

Procedures

The traditional "open" approach utilizes a median sternotomy or posterolateral thoracotomy. Lung volume reduction surgery can also be performed with VATS (video assist thoracic surgery). There is no evidence supporting the superiority of either approach, although VATS may have a lower incidence of respiratory failure. Most retrospective studies suggest a bilateral procedure has better outcomes but markedly increase post-operative morbidity. A unilateral procedure is therefore indicated in most circumstances. Stapled wedge resections have become the current gold standard of care.

How does LVRS work?

Detailed physiological studies showed that LVRS improves symptoms and exercise tolerance by multiple inter-related mechanisms including improved ventilatory capacity, decreased resting and dynamic hyperinflation and better diaphragmatic function. These positive effects can also benefit intra-pulmonary gas exchange and central hemodynamics (**Figure 1**).

Improvement in FEV_1 after LVRS has been found to be largely explained by increases in vital capacity. In other words, the less diseased lung after LVRS would expand and "resize" to better fit the chest cavity around it. Removal of destroyed, space-occupying alveoli improves the efficacy at which a given change in pleural pressure is transmitted to the remaining, more preserved alveolar units. Consequently, the lung becomes intrinsically more efficient in filling up more compliant units. Lung volume reduction

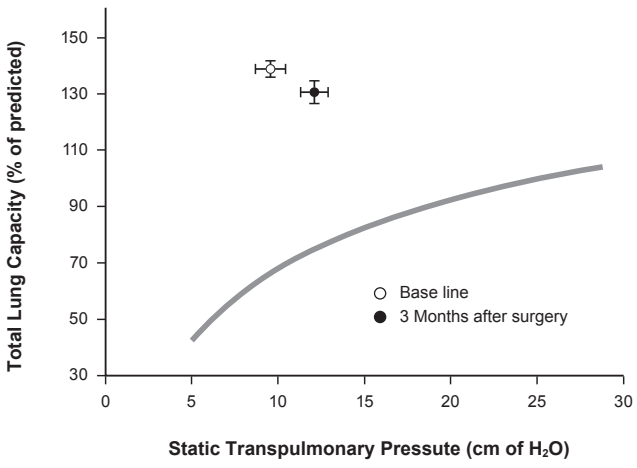

Figure 4. *Right and downward shift in the relationship between total lung capacity and transpulmonary pressure post-LVRS in a group of patients with advanced emphysema. This means an increased "coefficient of retraction" after surgery which decreases lung hyperinflation.*
Adapted from: Sciurba FC, Rogers RM, Keenan RJ, Slivka WA, Gorcsan J 3rd, Ferson PF, Holbert JM, Brown ML, Landreneau RJ. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N Engl J Med. 1996; 334: 1095-9.

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surgery can also increase the pressure driving maximal expiratory flow – the elastic recoil of the lung (**Figure 4**). Expiratory flow rates would then increase as a result of both volume recruitment and enhanced emptying pressure. The final consequences are lower residual volume (RV) and a downward shift of the operating lung volumes, *i.e.,* lung deflation (**Figure 1**). Similar to other lung deflating strategies, the diaphragm and other inspiratory muscles may benefit from reaching a more optimal length-tension relationship leading to greater maximal inspiratory pressures. These considerations are important to understand why patients with the highest RV/TLC ratio and larger amounts of macroscopically-evident emphysema pre-operatively are more likely to derive a physiological (and subjective) benefit from LVRS.

From the pulmonary gas exchange perspective, LVRS is variably associated with higher arterial partial pressure for O_2 (PaO_2) and/or lower $PaCO_2$. Increases in PaO_2 could happen if: 1) the excised tissue had overtly abnormal V/Q relationships and/or the post-LVRS improvement in lung mechanics alters V/Q; 2) LVRS improves alveolar ventilation and alveolar partial pressure for O_2 (PAO_2), *i.e.,* PaO_2 but unchanged $P(A\text{-}a)O_2$; or 3) the mixed venous circulation brings less deoxygenated blood to the lungs due to improved cardiac output and higher peripheral O_2 delivery and/or less O_2 is consumed in the periphery (e.g., due to lower respiratory muscle work) (**Figure 1**). **Figure 5** shows that all 3 factors are involved but with a greater relative importance of improved V/Q. On the other hand, decreases in $PaCO_2$ can be almost entirely explained by

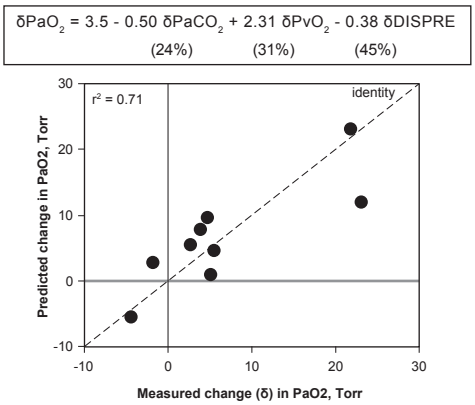

Figure 5. *Relative contribution of ventilation (represented by arterial partial pressure for CO_2 ($PaCO_2$)), extra-pulmonary factors (mixed venous partial pressure for O_2 ($P\bar{v}O_2$) and ventilation/perfusion inequality (DISPRE) for changes in PaO_2 induced by LVRS. This model explained about 70% of changes in PaO_2 after the procedure.*

Adapted from: Cremona G, Barberà JA, Melgosa T, Appendini L, Roca J, Casadio C, Donner CF, Rodriguez-Roisin R, Wagner PD. Mechanisms of gas exchange response to lung volume reduction surgery in severe emphysema.J ApplPhysiol (1985). 2011; 110:1036-45.

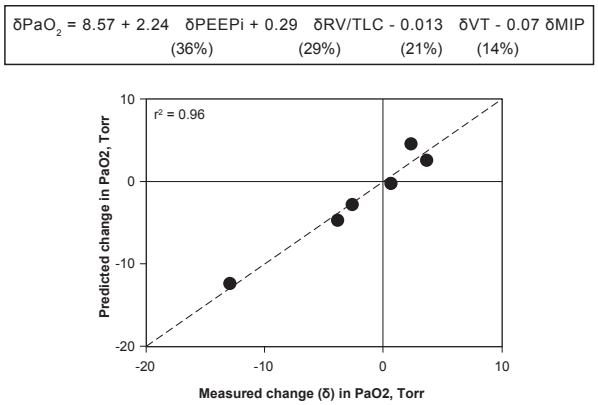

Figure 6. *Relative contribution of intrinsic positive end-expiratory pressure (PEEPi), residual volume / total lung capacity ratio (RV/TLC), tidal volume (VT) and maximal inspiratory pressure (MIP) for changes in arterial partial pressure for CO_2 ($PaCO_2$) induced by LVRS. Note that all contributors are directly or indirectly related to lower lung hyperinflation. This model explained about 95 % of changes in $PaCO_2$ after the procedure.*

Adapted from: Cremona G, Barberà JA, Melgosa T, Appendini L, Roca J, Casadio C, Donner CF, Rodriguez-Roisin R, Wagner PD. Mechanisms of gas exchange response to lung volume reduction surgery in severe emphysema.J ApplPhysiol (1985). 2011; 110:1036-45.

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improvement in lung mechanics (**Figure 6**) and neuromechanical coupling.

As previously mentioned, another potential benefit of LVRS relates to enhanced central hemodynamics. The exact mechanisms are unknown, but may involve lower mean intra-thoracic pressures, decreases in pleural pressure swings and recruitment of previously under-perfused lung vessels. The latter effect, in association with increased P_AO_2, may contribute to decrease right ventricular afterload. Of note, increases in FEV_1 after LVRS have been associated with a fall in mean pulmonary arterial pressure and changes in exercise capacity correlated with changes in left ventricular volume indices and a reduction in pulmonary arterial pressures at end-expiration. In fact, at least one study found that reduction in lung volumes during exercise after LVRS was associated with an increase in O_2 pulse (oxygen uptake/heart rate); an indirect index of stroke volume. Lung volume reduction surgery has also been associated with improvements in heart rate variability, suggesting a decrease in sympathetic tonus and a healthier autonomic balance. Improved hemodynamics and better arterial oxygenation would then increase peripheral O_2 delivery and mixed venous O_2 content (**Figure 5**) which collectively are likely to enhance arterial oxygenation, decrease breathlessness and increase exercise tolerance after LVRS (**Figure 1**).

From a clinical stand point, the most striking effect of successful LVRS (and bullectomy) is the alleviation of dyspnea. Although all of the above-mentioned mechanisms may contribute, there is well-established evidence that post-LVRS improvement in exertional dyspnea is associated with decrements in end-expiratory lung volume (EELV) and intrinsic end-expiratory positive pressure (PEEPi). As a consequence, the inspiratory muscles not only need to generate less pressure at the start of inspiration to overcome PEEPi but also their work is rewarded with greater volume displacement, i.e., better neuromechanical coupling (**Figure 3**).

Who are the best candidates for LVRS?

The National Emphysema Treatment Trial (NETT) was a landmark study that randomized more than 1200 patients to bilateral LVRS or best medical care. LVRS was associated with a lower risk of death than medical therapy in the 290 patients with upper lobe predominant emphysema and low exercise capacity. This subgroup was more likely to achieve ≥10W improvement in maximum exercise capacity and ≥8 unit improvement in St. George's Respiratory Questionnaire (SGRQ) score after 2 years of follow-up. In the 419 patients with upper lobe predominant emphysema and high exercise capacity, LVRS had no impact on survival. However, this subgroup also showed the same positive effects on exercise capacity and quality of life. In the 149 patients with non–upper lobe predominant disease and low exercise capacity, LVRS had no impact on survival or maximum exercise capacity, but quality of life was improved. Unfortunately, in the 220 patients with non–upper lobe predominant emphysema and high exercise capacity at baseline, LVRS increased the risk for death and had no effect on maximum exercise capacity or quality of life. Thus, the trial identified a subgroup of patients with heterogeneous emphysema and low baseline exercise capacity as having a reduced risk of death and clinically significant improvements. More recent studies confirmed that those with lower 6-min walking distance, more emphysema (but not homogenous/diffused), and greater hyperinflation at baseline are

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most likely to respond to LVRS. The beneficial effects of LVRS in the NETT were sustained with increased survival in the LVRS group at a median 4.3 years of follow-up. Nowadays, there is a trend towards performing staged unilateral LVRS separated by a period of 2 to 5 years to reduce operative risks and extend overall symptomatic benefit compared with bilateral LVRS at a single surgery.

Lung volume reduction surgery remains greatly under-utilized worldwide, possibly due to an erroneous interpretation that the NETT was negative and the surgery harmful. Although the NETT indicated that patients with FEV_1≤20% pred. with either carbon monoxide diffusing capacity (DL_{CO})≤20% pred. or a homogeneous emphysema pattern are at greater risk of complications and mortality, a substantial fraction of the patients did derive benefit from the intervention. The most common complications in the trial were arrhythmia, pneumonia, re-intubation, need of intensive care unit re-admission and prolonged mechanical ventilation. These findings prompted a list of general features of patients at greater risk of complications in whom the procedure is not advised or even contraindicated (**Table 2**).

Predictors of successful surgery / lower risk

- Heterogeneous emphysema
- Upper lobes predominance
- Poor exercise capacity after pulmonary rehabilitation

Predictors of unsuccessful surgery / greater risk

- FEV_1≤20% pred.
- DL_{CO}≤20% pred.
- Homogeneous emphysema
- Lower lobes predominance
- Major cardiopulmonary comorbidity, particularly heart failure and pulmonary hypertension
- Current smoking
- Chronic use of oral steroids
- Age >80 years
- Chronic bronchitic phenotype
- Chronic hypercapnia

Table 2. *Clinical, imaging and functional characteristics of patients more likely to benefit from LVRS and risk factors for the surgery.*

How to evaluate potential candidates for LVRS

As with the evaluation for bullectomy, HRCT should be used to carefully assess disease extension and for comparative analysis between upper versus lower lobe emphysema. Moreover, it would be helpful to assess coexisting problems, particularly a source of chronic infection or malignancy. Electrocardiogram, echocardiogram, dyspnea quantification, alpha-1-antitrypsin levels, quantitative ventilation/perfusion (V/Q) scan, full pulmonary function tests (including arterial blood gases and body plethysmography) and cardiopulmonary exercise testing with dyspnea measurements should be requested. Additional studies may be required according to patients' potential comorbidities, e.g., dobutamine-radionuclide scan and right heart catheterization.

C4.
Surgical Approaches for Lung Volume Reduction

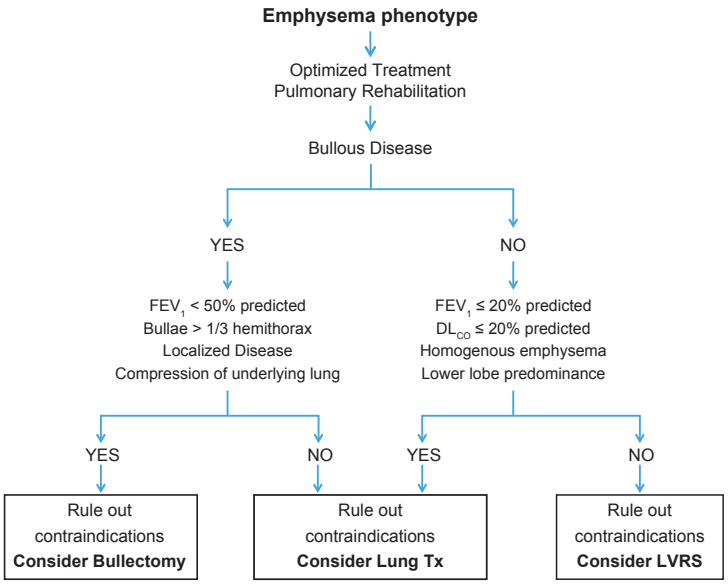

Figure 7. *Schematic algorithm for a practical evaluation of potential candidates for a surgical approach to lung hyperinflation in patients with COPD. FEV_1: forced expiratory volume in 1 second; DL_{CO}: lung diffusing capacity for carbon monoxide; Tx: transplantation; LVRS: lung volume reduction surgery.*

CONCLUSIONS

The decision to refer a patient with advanced emphysema for any surgical approach should be made after careful judgement of the benefits and risks in an aged population where multiple morbidities may coexist. The best decision is usually reached by combining clinical, structural and functional data in a motivated patient in whom pharmacological and non-pharmacological treatments have been appropriately optimized (**Figure 7**). Pulmonary transplantation remains the last alternative for debilitated patients with poor prognosis and/or those not fitting the anatomical and clinical pre-requisites for a favourable response to LVRS.

C4.
Surgical Approaches for Lung Volume Reduction

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C5.
Medical Lung Volume Reduction

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C5.
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Key Points

1.
Bronchoscopic lung volume reduction may become an alternative to surgical lung volume reduction method(s), to reduce hyperinflation.

2.
Except for the airway bypass stents, all other methods have shown beneficial effects reducing hyperinflation; improving lung function, 6-minute walking distance and health related quality of life equivalent to lung volume reduction surgery.

3.
However, bronchoscopic lung volume reduction methods are still under investigation, and have not yet been approved by the FDA for the treatment of severe emphysema.

4.
A major problem is collateral ventilation due to incomplete fissures. Common adverse events are pneumothorax and COPD exacerbations.

C5.
Medical Lung Volume Reduction

INTRODUCTION

Reduction of the damaged areas of the lung is a very old method of medicine. During the last century, before the discovery of anti-tuberculosis medications, a common technique was medical therapeutic pneumothoracis: by introducing air into the thoracic cavity, a compression of the lung occurred, reducing the tuberculus cavities, leading to healing.

This idea had been reintroduced by the results of lung volume reduction surgery (LVRS) for the treatment of severe emphysema (see chapter C4).

However, LVRS has significant limitations; such as, benefits confined to a very selective group, attendant morbidity and increased early mortality.

Bronchoscopic lung volume reduction (BLVR) is a method under development for a less invasive, less expensive, low morbidity and mortality alternative technique to LVRS.

Its rationale is the same as LVRS: to reduce the most damaged areas of the lung to decrease hyperinflation and thus, to improve respiratory mechanics and gas exchange mechanisms, as well as improvement in the cardinal symptom of dyspnea, exercise capacity and health-related quality of life (QoL).

However, these techniques are still under investigation, being tested in small early-phase clinical trials and not having been approved by the U.S. Food and Drug Administration (FDA) for the treatment of emphysema, although they have shown potential benefits in lung function, exercise capacity and QoL.

METHODS

There are five different methods of BLVR:

1. One way valves;
2. Sealant /hydrogens (BioLVR);
3. Coil implants (LVRCs);
4. Airway bypass stents; and
5. Bronchial thermal vapor ablation (BTVA) therapy.

One-way Valves

These valves, when positioned in target airways, allow the exit of air from distal airways, while preventing the inspired air to enter these airways (**Figure 1**).

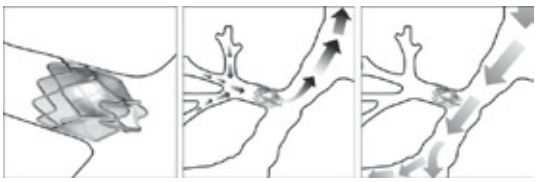

Figure 1. *The general principles of one-way valves. (Left) Positioning of the valve into the bronchi of the affected area. (Middle) Air is exhaled from the affected area (collapse).*
(Right) Inhalation is not going into the affected area.

There are two commercially available one-way valves, which are designed to be removable:

1. The Spiration® IBV is an umbrella like valve deployed via the working channel of the flexible bronchoscope. The main benefits were seen in QoL, without notable changes in lung reduction or 6-minute walking distance (6MWD). (**Figure 2**)
   The common adverse events were pneumothorax, bronchospasm and pneumonia.

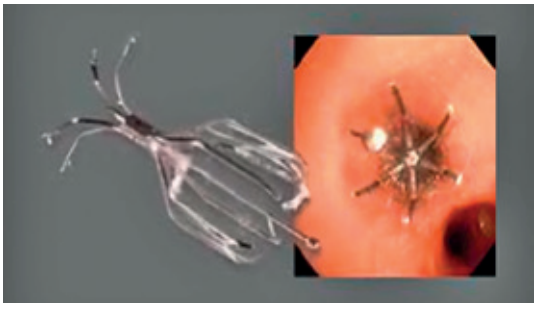

Figure 2. *The Spiration® one-way valve.*

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Medical Lung Volume Reduction

2. The Zephyr® Valve is a duck-billed silicone valve that anchors in the airways, creating an airtight seal with the bronchial wall. It allows trapped air and secretions to exit the valve during exhalation. This valve is inserted in the target airways by the flexible bronchoscope, as previously described. The Zephyr valve had been shown to improve forced expiratory volume in 1 second (FEV_1) and 6MWD, but adverse effects include increase in exacerbations and hospitalizations (**Figure 3**).

Figure 3. *The Zephyr® one-way valve.*

The major limitation of one-way valves is the presence of collateral ventilation that does not allow atelectasis of the lung area distal to the valve. A catheter mediated device (Pulmon X) to measure inter-lobar collateral ventilation has been developed, and it has been suggested that its use prior to positioning of the valves ensures best results.

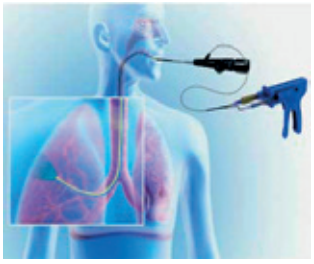

Figure 4. *The biologic lung volume reduction method.*

Biologic Lung Volume Reduction (BioLVR) (Figure 4)

The BioLVR therapy is a bronchoscopic administration of fibrinogen suspension and thrombin solution into the targeted airways separately. On contact, those substances polymerize into hydrogel that causes a local inflammatory reaction; leading to remodeling of the airways, occlusion and atelectasis with volume reduction seen 4-6 weeks later. The results of a number of clinical studies showed an improvement in FEV_1, a reduction in residual volume and the ratio of residual volume/total lung capacity (RV/TLC), reduced dyspnea scores, and improved QoL (St. George's Respiratory Questionnaire [SGRQ]). The common adverse effects were fever, leukocytosis, and malaise and COPD exacerbations. In order to avoid using human blood products, a synthetic system was developed (The AeriSeal® System) (**Figure 4**). This system uses hydrogel foam that biodegrades as a surfactant, leading to atelectasis in order to increase the efficacy of this method. BioLVR efficacy is also affected by collateral ventilation; thus, fissure integrity is an important factor that should be evaluated before the procedure.

Coil Implants (LVRCs) (Re -Pnew)

When the coil is placed into the airway, it conforms into its predetermined shape and by bending in the lumen and causing compression of the adjacent lung tissue, creates local LVR. (**Figure 5**). It had been shown that this procedure improved SGRQ, FEV_1, RV and 6MWD. Exacerbations and pneumothorax are the common adverse events. It must be noted that there are very few studies using coils for BLVR.

C5.
Medical Lung Volume Reduction

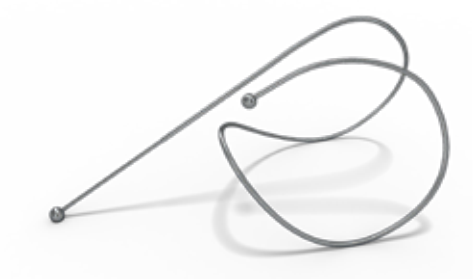

Figure 5. *Coil implants (Re-Pnew).*

Airway Bypass Stents (Figure 6)

Airway bypass stents have been developed to create and sustain passages between bronchi and emphysematous lobes. This procedure usually involves the placement of three to four drug eluting stents in order to create supported fenestrations between the bronchial tree and the damaged lung parenchyma. The procedure needs a Doppler probe to find non-vascular sites, and, of course, a highly skilled bronchoscopist. A multi-center bronchoscopic study (Exhale airway stents for Emphysema) [EASE]) in homogeneous emphysema patients had shown initial benefits in lung function and QoL, that were not sustained at 6 or 12 months.

Figure 6. *An airway bypass stent.*

Bronchoscopic Thermal Vapor Ablation (Figure 7)

This method uses heated water to induce thermal injury, leading to a local inflammatory response resulting in permanent fibrosis and atelectasis. It uses a balloon catheter that seals the airways, while the predetermined water vapor is administered to the emphysematous lobes. This method reduces lung volume measured radiographically, improves FEV_1, reduces RV, and increases 6MWD, BODE (body mass index, airflow obstruction, dyspnea and exercise capacity) index and SGRQ. Exacerbation of COPD was the most common adverse event.

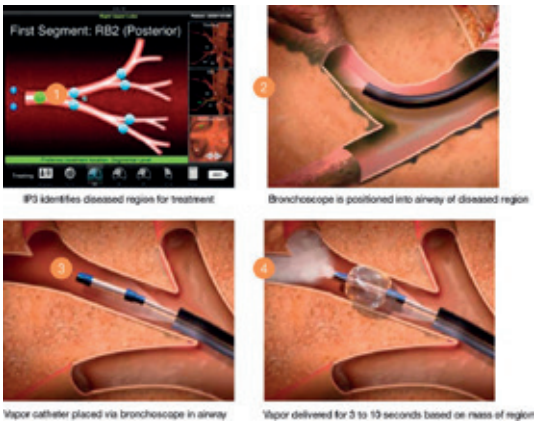

Figure 7. *Bronchoscopic Thermal Vapor Ablation.*

C5.
Medical Lung Volume Reduction

CONCLUSIONS

A recent meta-analysis of the efficacy of bronchoscopic lung volume reduction methods concluded that, except for the airway bypass stents, all other methods showed efficacy in primary outcomes. BioLVR showed the most significant findings and was least associated with major treatment related complications. Finally, it was stated that BLVR showed non-inferiority, if not equivalence, compared to surgical LVR. However, it must be emphasized that, all the above methods, although promising, are still under investigation and not approved by the regulatory agencies for the treatment of advanced emphysema.

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List of abbreviations (alphabetically)

Acetylocholine	Ach
Acute exacerbations of COPD	AECOPD
Acute respiratory distress syndrome	ARDS
Adenosine diphosphate	ADP
Adenosine triphosphate	ATP
Airway pressure	P_{ao}
Alpha-1 Antitrypsin	A_1AT
Alveolar partial pressure for O_2	PAO_2
American Thoracic Society/European Respiratory Society	ATS/ERS
Anti-DNase B	ADB
Arterial carbon dioxide pressure	$PaCO_2$
Arterial oxygen pressure	PaO_2
Australian Respiratory Early Surveillance Team for Cystic Fibrosis	AREST-CF
Barometric pressure in cmH_2O	Pb
Biologic lung volume reduction	BioLVR
Body mass index	BMI
Body mass index, airflow obstruction, dyspnea and exercise capacity	BODE index
Breathing frequency	F_b
Bronchial thermal vapor ablation	BTVA
Bronchoscopic lung volume reduction	BLVR
Calcium	Ca^2
Calcium ions	Ca^2+
Carbon dioxide	CO_2
Carbon monoxide diffusing capacity	DL_{CO}
Cardiopulmonary exercise tests	CPET
Chronic obstructive pulmonary disease	COPD
Chronic Respiratory Disease Questionnaire	CRQ
Computed tomography	CT
Continuous positive airway pressure	CPAP
Corrected airway pressure	cP_{aw}
Cystic fibrosis	CF
Cystic Fibrosis Transmembrane Conductance	CFTR
Diaphragm electromyography	EMGdi

List of abbreviations (alphabetically)

Dynamic compliance of the lung	Cdyn
Dynamic hyperinflation	DH
Dynamic lung hyperinflation	DH
End-expiratory lung volume	EELV
End-inspiratory lung volume	EILV
Esophageal pressure	P_{eso}
Esophageal pressure	P_{es}
European Network for Understanding Mechanisms of Severe Asthma	ENFUMOSA
Exhale airway stents for Emphysema	EASE
Expiratory flow limitation	EFL
Expiratory reserve volume	ERV
Forced expiratory flow 25–75%	$FEF_{25–75\%}$
Forced Expiratory Flow at 50%	$FEF_{50\%}$
Forced expiratory volume in 1 second	FEV_1
Forced vital capacity	FVC
Functional residual capacity	FRC
Functional residual capacity	FRC
Gastric pressure	P_{ga}
Global Initiative for Chronic Obstructive Lung Disease	GOLD
High-resolution computed tomography	HRCT
Inert gas (helium) dilution	FRC_{He}
Inhaled corticosteroid	ICS
Inorganic phosphate	Pi
Inspiratory capacity	IC
Inspiratory pressure	P_{insp}
Inspiratory pressure support	IPS
Inspiratory reserve volume	IRV
Inspiratory time	Ti
Inspiratory vital capacity	IVC
Intensive care unit	ICU
Intrinsic positive end-expiratory pressure	PEEPi
Joule	J
Left ventricular	LV
London Cystic Fibrosis Collaboration	LCFC
Long acting ß2-agonist	LABA

List of abbreviations (alphabetically)

Long-acting muscarinic antagonist	LAMA
Lung hyperinflation	LH
Lung volume	V_L
Lung volume reduction coil	LVRC
Lung volume reduction surgery	LVRS
Magnesium	Mg^2
Magnetic resonance imaging	MRI
Maximal expiratory pressure	MEP
Maximal inspiratory pressure	MIP
Maximal inspiratory pressure	PI_{max}
Minimal clinically important difference	MCID
Minute ventilation	V'_E
Multi-Ethnic Study of Atherosclerosis	MESA
n-acetylcysteine	NAC
National Emphysema Treatment Trial	NETT
Neonatal Chronic Lung Disease	CLD
Nitrogen	N_2
Nitrogen washout	FRC_{N2}
Non-invasive ventilation	NIV
Oral phosphodiesterase-4	PDE4
Oxygen	O_2
Peak work rate	Wpeak
Physiological dead space	V_D
Plethysmography	FRC_{pleth}
Positive end-expiratory pressure	PEEP
Pressure-volume chest wall curve	$Pel_{(cw)}$
Pressure-volume chest wall curve	P_{cw}
Pressure-volume lung curve	$Pel_{(L)}$
Primary Ciliary Dyskinesia	PCD
Proportional assisted ventilation	PAV
Provocative concentration causing a 20% drop in FEV_1	PC_{20}
Pulmonary gas trapping	RV, RV/TLC
Pursed lip breathing	PLB
Quality of life	QoL
Quantitative ventilation/perfusion	V/Q

List of abbreviations (alphabetically)

Quartile	Q)
Randomized clinical trials	RCTs
Ratio of tidal volume to inspiratory capacity	V_T/IC
Relaxation volume	V_r
Required ventilation	V_E
Residual volume	RV
Residual volume/total lung capacity	RV/TLC
Respiratory distress syndrome	RDS
Respiratory neural drive	RND
Respiratory syncytial virus	RSV
Slope of body box volume and alveolar pressure line during panting	ΔV/ΔP
Slow vital capacity	SVC
St. George's Respiratory Questionnaire	SGRQ
Thoracic gas volume	TGV
Tidal volume	V_T
Total lung capacity	TLC
Total respiratory system	P_{rs}
Transdiaphragmatic pressure	P_{di}
Transition Dyspnea Index	TDI
Trigger sensitivity	P_{tr}
Upper limit of normal	ULN
Video-assisted thoracoscopic surgery	VATS
Vital capacity	VC
Work of breathing	WOB
6-minute walking distance	6MWD

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Chapter C1

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HYPERINFLATION OF THE LUNG
AND ITS MANAGEMENT

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