



# **COPD**

## **DISEASE & TREATMENT OPTIONS**

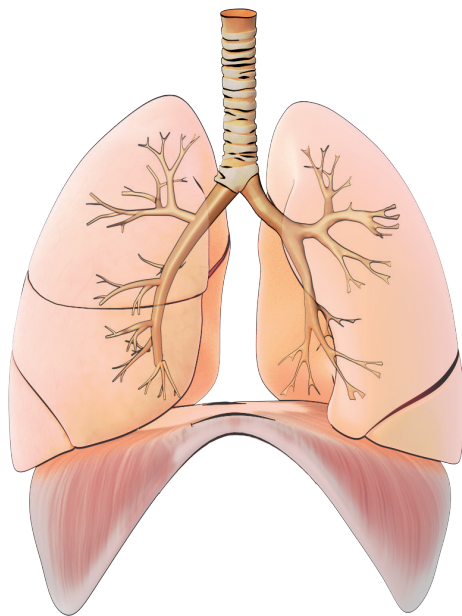
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# COPD – THE DISEASE

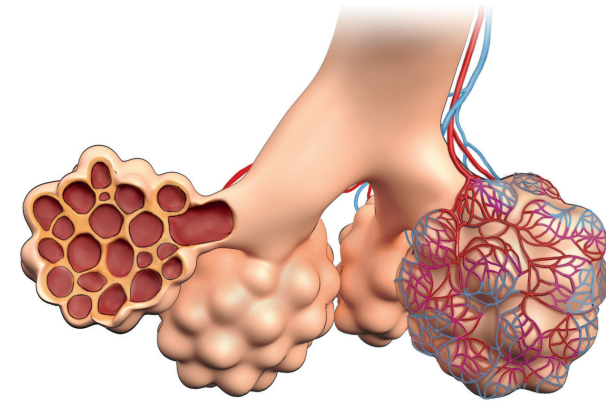
## THE RESPIRATORY SYSTEM

When we inhale, air enters the mouth and the nose and passes through the windpipe (trachea), and further out to the right and the left bronchus (air tube). Each bronchus extends into a lung where they branch out like a tree. The branches of the bronchial tree continue to divide into smaller bronchi and the further into the lungs they reach out, the smaller they become and the smallest air tubes are called the bronchioles. The bronchioles will eventually lead to the respiratory bronchioles, which in turn will end in an air sac (alveolar sac). The bronchial tree serves as the means of transport through which air passes in and out and the alveolar sacs are the place for gas exchange.



*The lower respiratory system including the windpipe, bronchial tree and the lungs. Air travels throughout the respiratory system where it gets moistened, warmed and cleaned from particles.*

The alveolar sacs look like a cluster of grapes and when looked at in cross section, one could see that the “grapes”, the pulmonary alveoli, are small, interconnected compartments within the air sacs. On the outside of the alveolar walls runs a thin and dense layer of capillaries, which is site for gas exchange between the lungs and the blood. Inhaled oxygen diffuses through the alveolar walls into the blood vessels where it gets transported out to the cells, the waste product, carbon dioxide, will be transported out via the veins and back to the lungs to be exhaled.



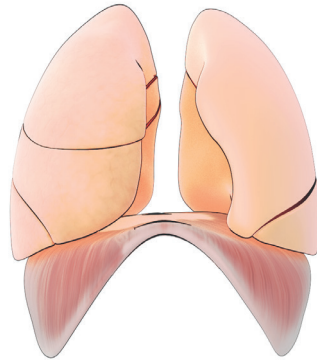
*The alveolar sacs are the respiratory division of the lungs. It is between these very thin walls where the gas exchange between the lungs and the blood occurs.*

An efficient gas exchange is vital and the human lung is normally made up of 350 millions pulmonary alveoli making up a large surface area (60-80 m<sup>2</sup>) for oxygen and carbon dioxide exchange [1].

One important building block of the alveolar sacs is the protein called elastin [2]. It gives them their elastic property and enables them to expand and get filled with air upon inhalation and to squeeze out the air when exhaling. The inherent elasticity of the lungs is essential for an efficient breathing and so are also the respiratory muscles, which assist in filling and emptying the lungs. The biggest and most important muscle involved in breathing is the diaphragm, which is located directly below the lungs. It moves down and flattens when inhaling, and flexes upward to its relaxed state when exhaling, emptying the lungs from air [3],[4].

The lungs are divided into five different lobes by interlobar fissures. The right lung consists of an upper-, middle- and a lower lobe while the left lung only has an upper- and a lower lobe, providing room for the heart [1].

The diaphragm has a dome shape when relaxed and contracts and presses downwards upon inhalation [5].



## COPD

Chronic Obstructive Pulmonary Disease, or COPD, is a term describing a couple of chronic lung diseases where the ability to breathe has been decreased. COPD is a major health problem and it is one of the leading causes of death worldwide. The world health organization, WHO, has predicted that COPD will be listed as the third leading cause of death by 2030 [6],[7].

COPD is a result of a long-term inflammation causing the small airways to become narrowed and lung tissue to be destroyed.

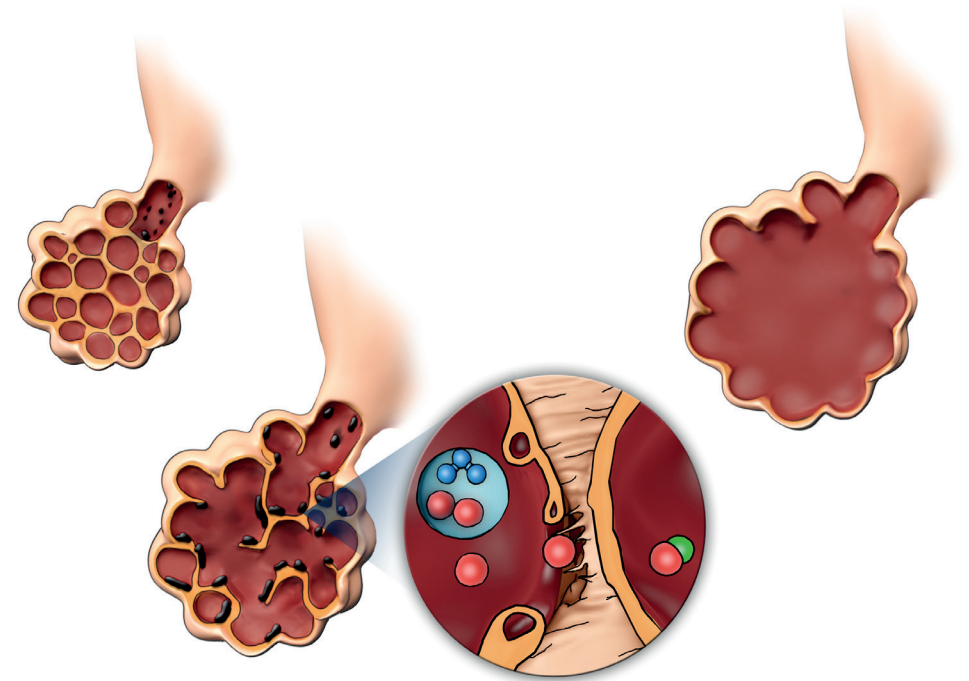
Chronic bronchitis and emphysema are both COPD and individuals with COPD do often suffer from a combination of both of the conditions.

Chronic bronchitis is a disease in the small airways where the bronchioles have become narrowed and where there is an overproduction of mucus or sputum. The first symptoms of chronic bronchitis is chronic cough and shortness of breath. COPD is however asymptomatic for a long period of time and there is a time gap from when the inflammatory process starts until the first symptoms begin to show [8], [9].

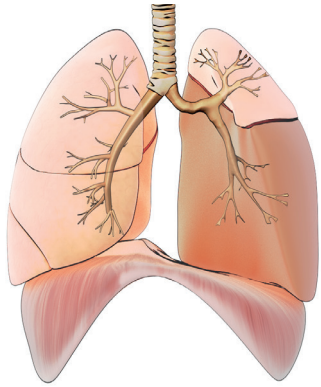
## EMPHYSEMA

Emphysema is characterized by the destruction of the inner walls of the air sacs. The degradation happens slowly over time and as the air sacs lose their elastic property, air starts to get trapped and due to reduced elastic recoil the air needs to get squeezed out which makes breathing difficult. The mechanism behind the destruction of the air sacs is not yet fully understood but it is believed to be

a result of an inflammatory response initiated by particles or toxins (e.g. from tobacco smoke). When these particles enter the lungs, cells recruited from the immune system and molecules called proteases, e.g elastases are released. These molecules will eventually start to break down the elastin in the alveoli walls if not being blocked by anti-proteases. One anti-protease involved in this process is alpha-1-antitrypsin, which serves as a natural protection and inhibits the proteases from destroying the tissue of the air sacs. Some people are born with a genetic disorder which causes less alpha-1-antitrypsin to be produced and this group runs a higher risk of developing emphysema [10], [11], [12].



Long-term exposure to particles or toxins can initiate an inflammatory reaction within the lungs. Cells recruited from the immune system release proteases as a response to the foreign particles. The proteases will start to degrade the healthy tissue within the air sac if the inflammatory reaction remains over a long period of time. Alpha-1-antitrypsin is an anti-protease that hinders the inflammatory process.



*As air is getting trapped inside the alveolar sac, the lungs start to become hyperinflated and the lungs will press down against the diaphragm causing it to flatten.*

As the elasticity of the air sacs becomes reduced, there will be an over all reduction of the lungs' capacity to move air in and out. Air getting trapped inside the air sacs is referred to as "hyperinflation" and when this happens in one diseased lobe it will expand and press against the surrounding healthier lobes reducing their capacity. When the disease has progressed to a certain degree, the overinflated lungs will press down against the diaphragm causing it to flatten. A vicious circle has begun and the first symptoms of emphysema are the experience of breathlessness, dyspnea, and a lowered exercise capacity. As the degradation of the alveoli walls continues, the surface area for gas exchange becomes reduced resulting in an imbalance in gas exchange between the lungs and the blood. At this stage, symptoms like fatigue and breathlessness when performing normal activities like walking up the stairs start to appear [7], [13].



1. **Chronic cough and mucus production**
2. **Breathlessness when exercising**
3. **Tiredness and lack of fitness**
4. **Constant breathlessness, lower quality of life, exacerbation and comorbidities, weight loss**
5. **Social isolation and depression**

Causes COPD
Tobacco smoke
Occupational dusts
Toxic fumes and vapors
Secondary tobacco smoke
Alpha 1 anti-trypsin deficiency

*Smoking is the major cause of emphysema and COPD. Long-term exposure to occupational dusts, fumes, vapor or air pollutions can also cause the disease as well as some genetic disorders [8],[9].*

*A chronic cough, large mucus production and wheezing are some of the first symptoms of COPD as well as breathlessness upon exertion. As the disease progresses the breathlessness becomes worse and people with COPD do also start to experience tiredness. When the gas exchange has been severely impaired, comorbidities and exacerbations (infections) are more common and the overall worsening in health condition may lead to social isolation and depression [7],[14].*

### Exacerbations

As the disease progresses the symptoms become worse and the frequency of exacerbations increases. An exacerbation is defined as sudden change from the day-to-day symptoms, often including attacks of breathlessness, increased coughing and mucus production. An exacerbation is often caused by an infection and requires a change in medication. [7], [15].

### Comorbidities

People suffering from COPD do often get diseases directly or indirectly associated to their COPD. Examples of common comorbidities are cardiovascular diseases due to insufficient gas exchange, osteoporosis as a side effect of some of the medications, lung cancer due to smoking, diabetes or lung infections. Another common comorbidity is depression [8],[15].



## DIAGNOSTICS

COPD is frequently under-diagnosed because the first symptoms do not show until the disease has reached a late stage. The sooner a person knows they have emphysema the sooner he or she can start to treat the symptoms in order to slow down the disease progression [9].

There are different ways to diagnose emphysema. The different methods are often combined in order to determine the disease stage and its spreading. A diagnosis is important to decide on a suitable treatment.

The group at risk are those who have a long history of smoking, middle aged or older, who have started to experience shortness of breath, chronic cough, overproduction of mucus and/or who have a history of COPD within the family. This group should visit a doctor to get a pulmonary function test [12].

### PULMONARY FUNCTION TESTS (PTF)

#### SPIROMETRY –LUNG CAPACITY TEST

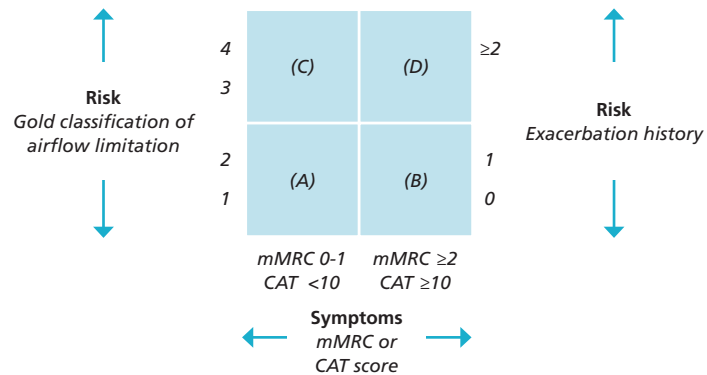
Spirometry is a common pulmonary function test used to diagnose emphysema. It is quick and simple to do. The person is asked to blow out as hard as he or she possible can into a mouthpiece connected to a machine that measures the lung capacity. A spirometer measures how much air the lungs can hold and how fast they can be filled and emptied. The Forced Expiration Capacity ( $FEV_1$ ) is defined as the maximum amount of air someone can blow out during the first second of exhalation. The  $FEV_1$  is commonly used as an indicator on the severity of the disease and the lower the value the worse the lung capacity. Other parameters measured by a spirometer are Forced Vital Capacity (FVC), which is the maximum amount of air blown out during one exhalation.

Spirometry is performed after taking bronchodilators and the results are compared with predicted normal values, which are based on the gender, height and age of the person performing the test [8],[16].

It is important to follow the instructions given by the doctor to get the most accurate test results.

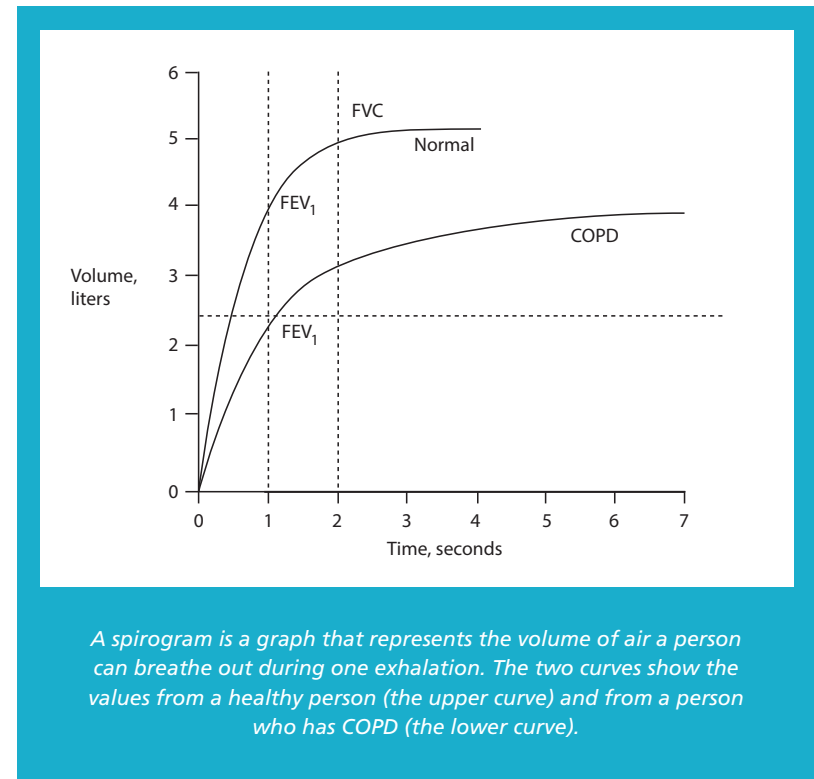
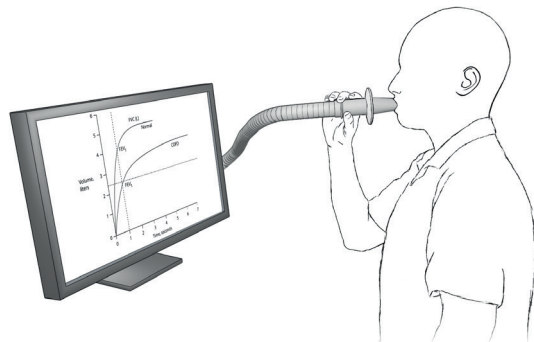
FEV <sub>1</sub> value (and a FEV <sub>1</sub> /FVC < 70%)	Disease Stage
FEV <sub>1</sub> ≥ 80% predicted	I Mild
50 % ≤ FEV <sub>1</sub> < 80% predicted	II Moderate
30 % ≤ FEV <sub>1</sub> < 50 % predicted	III Severe
FEV <sub>1</sub> < 30% predicted	IV Very Severe

GOLD has classified the different disease stages based on predicted FEV<sub>1</sub> values. The FEV<sub>1</sub> values are measured after taking bronchodilators [8].



In addition, GOLD has another classification of the different disease stages, A-D. This is based on the spirometric values from the previous table (FEV<sub>1</sub>) combined with the number of exacerbations per year and the scores from the CAT or mMRC questionnaire. In both of these questionnaires you are asked to answer questions about your COPD related symptoms [12].

The patient is asked to breathe into a mouthpiece and to make force-breathing maneuvers in order to test the FEV<sub>1</sub> and FVC values.



A spirogram is a graph that represents the volume of air a person can breathe out during one exhalation. The two curves show the values from a healthy person (the upper curve) and from a person who has COPD (the lower curve).

## BODY PLETHYSMOGRAPHY

While a spirometer measures the ability to fill and empty the lungs in respect to a normal value, a body plethysmograph measures how much air (in liters) that has been trapped within the lungs. This is called the residual volume (RV) and it is the volume of air in the lungs that cannot be exhaled. Since this volume increases as the emphysema progresses, patients with emphysema will have a larger residual volume compared to healthy lungs. The residual volume of healthy lungs is 100% and this reference value is based on the RV of a normal healthy population [17],[18].



*A body plethysmograph is a glassed airtight box in which you sit and breathe into a mouthpiece. The doctor measures the amount of air that is entering and emptying the lungs.*

### **The 6 minutes walk test**

A 6 minutes walk test (6MWT) tests the exercise capacity and measures the distance a person can walk for a total of 6 minutes. The test should be performed on a flat, hard surface without obstacles. During the test, the oxygen saturation and pulse are measured and recorded by a pulse oximeter. The test is used to decide upon a treatment and to monitor the disease progression.

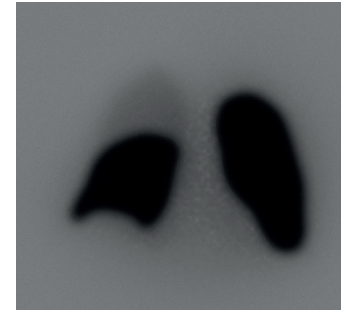
### **Imaging techniques**

In addition to the pulmonary function tests, there are a couple of imaging techniques used to diagnose emphysema. The advantage of the imaging techniques is that the disease can be localized and characterized.

### **Scintigraphy, ventilation / perfusion scan**

A ventilation/ perfusion scan is performed to evaluate two things: how well the air is circulating in the lungs (ventilation) and how well the blood circulation

within the lungs is working (perfusion). This technique makes it possible to determine the spreading of the disease. In contrast to the other imaging techniques, where a low dose of external radiation is required to create the image, scintigraphy, which is the technique used in the ventilation /perfusion scan projects an image from internal radiation using a so called gamma camera. Radioisotopes (low-risk) are injected to the blood stream for the perfusion scans and inhaled as a gas for the ventilation scans[19].



*A perfusion scan of the lungs showing the distribution of the blood circulation within the lungs. This image is showing a low perfusion in the right upper lobe.*

### **Chest X-ray**

A chest X-ray scan is an image of the chest and it can show if the ribcage has expanded due to hyperinflation and if the diaphragm has been flattened. A chest X-ray can also detect other conditions [20],[21].

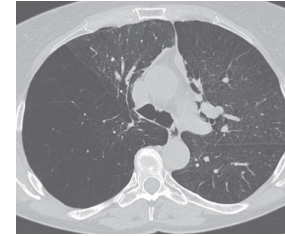


*An X-ray scan showing the ribcage, lungs, heart and diaphragm. Bones are very dense and allow little radiation to pass through, therefore white, while less dense air-filled tissue appears darker.*



## THORAX CT

Computed Tomography (CT) has become the method of choice when details about the disease spreading are required. CT is used to diagnose patients with severe or very severe emphysema who may be considered as a candidate for surgery or other less invasive treatments. Multiple images of thin sections are taken and the scans can detect diseased lobes and visualize the spreading of damaged lung tissue. CT is more accurate in comparison to chest X-ray [20],[21].



*The resolution of a CT is better compared to the regular chest X-ray. Here is a cross sectional scan showing the left and the right lung.*

Technique	What is tested?	Why?
Spirometry	FEV <sub>1</sub> and FVC, and their ratio	To measure the lung capacity, monitor the disease and exclude other diseases
Body Plethysmography	Residual volume (RV)	Determine how much air that has been trapped inside the lungs and to measure the degree of hyperinflation
Scintigraphy Ventilation / Perfusion scan	Gas diffusion and blood circulation	To specify what part of the lungs that still have a functioning gas exchange and blood circulation
6 Minute Walk test	Exercise capacity, stamina	To determine if the patient can be considered as a candidate for some treatments and as a follow-up on how the patient has responded to a treatment
Chest X-ray	An image of the ribcage including the heart, lungs and diaphragm	To get an overview of the ribcage including the lungs, heart, and diaphragm
CT	Detailed thin images of the lungs	To visualize the disease spreading, and to diagnose emphysema

What is an indication of severe emphysema	The technique in brief
FEV <sub>1</sub> values below 50% than predicted	Spirometry tests relative volumes, the results are compared with a normal value based on height, gender and age
RV over 170% TLC>150% is considered as severe hyperinflation	Body plethysmography measures absolute volumes. Boyle's law is used to calculate the residual volume (RV) and the total lung capacity (TLC)
Low gas diffusion and blood circulation	Radioisotopes are injected or inhaled and detected by a gamma camera and an image is acquired
300 meters or less	A test performed on a flat surface, timed and monitored by a healthcare professional
Compressed diaphragm, widened chest due to hyperinflation	A beam of X-rays is released from a radiation source, the rays pass through the body and are collected by a detector that projects an image. Since different organs and tissues have different densities, the radiation will be absorbed differently. The whiter they appear, the denser the organ
Hyperinflation and destroyed alveolar sacs	In computer tomography (CT), X-rays are also used but from multiple angles enabling a computer to acquire a detailed 3D image

# TREATMENTS

Emphysema is a chronic disease and a result of destroyed tissue. There is currently no cure to the disease but there are several treatment options available, which can decrease the symptoms and make it easier to breathe. Treating the disease can also slow down the progression and improve the exercise capacity and the quality of life.



- 1. Stop smoking**
- 2. Exercise, keep active to improve breathing capacity**
- 3. Medical management**
- 4. Oxygen therapy, non invasive ventilation**
- 5. Lung volume reduction or transplantation**

*There are different treatment options and various measures which can be taken to prevent the disease from getting worse and to treat the symptoms.*

## STOP SMOKING

The first thing to do if diagnosed with a COPD is to quit smoking in order to stop the disease progression. Even if you have been smoking for many years and the inflammatory process has already gone far, quitting will stop it from getting worse and it will also reduce the frequency of exacerbations and lower the risk from getting many of the comorbidities such as lung cancer and cardiovascular diseases.

If the disease has been brought on by other factors such as occupational gases or toxins, you should try to reduce or stop this exposure [22].

## GETTING HELP

There are many nicotine replacements therapies available, which could help you with your addiction. A number of those can be bought at the local pharmacy. Examples of nicotine replacements are gums, patches, lozenges, tablets, nasal sprays and inhalers. The best option for you should be discussed with your pharmacist or your doctor. There are also other alternatives, which can be prescribed by a doctor and some people might need counseling in order to quit [23].

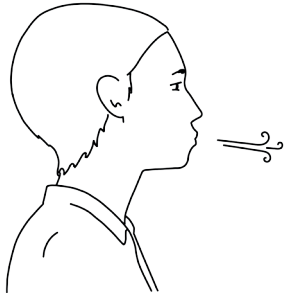
[If you are suffering from a cardiovascular disease, you should discuss this with your doctor before choosing a nicotine replacement therapy since they can affect your blood pressure.]

## PULMONARY REHABILITATION, DISEASE MANAGEMENT PROGRAM

Pulmonary rehabilitation is an individualized educational- and exercising program where you can learn about how to manage the disease and lower the frequency of exacerbations. The program also covers the social aspects of living with emphysema and you will be able to meet with other people suffering from COPD during the classes.

The aim of the exercise part of a pulmonary rehabilitation program is to improve your physical strength in order for you to cope with your breathlessness. It is important to continue doing these exercises even after the rehabilitation.

## LEARN HOW TO CONTROL YOUR BREATHING AND BREATHE MORE EFFICIENTLY

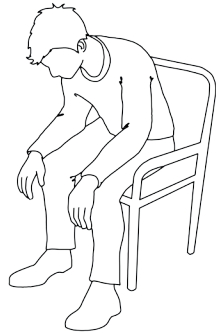


### Pursed lip breathing

Can help to reduce breathlessness, empty the lungs from trapped air and slow down the breathing rate. To perform this exercise, keep your mouth closed and inhale through your nose, purse your lips and breathe out slowly. By pursing the lips a back pressure is created enabling the airways to open up and trapped air to be pushed out.

### The forward leaning position

Can relieve breathlessness by improving the capacity of the diaphragm



### Inspiratory muscle training

Helps to train the breathing muscles e.g. the muscles in the neck and shoulders, enabling those to compensate for the flattened diaphragm. The person inhales air through a mouthpiece and adapter, which provides resistance hence training the muscles.

### Resistance training/Walking

Keeping fit is important and will help you to manage your lung condition better.



## MEDICAL MANAGEMENT

There is a wide range of pharmaceutical treatments available on the market and since COPD is a complex disease with several symptoms and many comorbidities, the different medical treatments can be combined to reach a better effect. The effect may also vary between individuals and it is therefore important to discuss the best treatment options with a doctor. Some medications are taken daily as a life long treatment (maintenance medications), while others are only taken when experiencing exacerbations (as-needed).

As mentioned in the previous chapter, persons who have emphysema do often have chronic bronchitis as well and they are therefore in need of medications that will help them to dilate the airways.

### DRUG DELIVERY SYSTEMS

The medications can be taken in different ways and forms. They can be taken as tablets, inhaled as liquids or as dry powders or they can sometimes be injected.

Most of the medications are inhaled because they will then reach their target, the lungs, fast. A smaller dose is also often required since the drug does not have to go out in the entire body.

### BRONCHODILATORS

Bronchodilators are a group of medications which cause the muscles in the narrowed airways to relax and allow more air to pass through making it easier to breathe.

There are three main groups of bronchodilators, beta<sub>2</sub>-agonists, anticholinergics and theophyllines, all of them dilate the airways but they act in different ways.

The bronchodilators are also classified according to how fast and how long they are effective. There are short-acting and long-acting bronchodilators. The recommendation for people suffering from COPD is to use inhaled long-acting bronchodilators, in order to get a lasting effect. The short-acting bronchodilators can however be useful to treat exacerbation when the patient experiences acute breathlessness. Inhaled medications are preferred to tablets or injections since they have fewer side effects.

Consult with your doctor on what option will be best for you.

## BETA<sub>2</sub>-AGONISTS

The beta<sub>2</sub>-agonists relax the muscles in the small airways (bronchioles) and enable air to pass through more easily. The side effects for this group are, due to the muscle relaxing properties that other muscles such as the heart muscles and the skeletal muscles can be affected causing a faster heartbeat or shivering.

## ANTICHOLINERGICS

The anticholinergic group mainly affects the larger airways. They prevent the muscles in the bronchi from contracting.

It takes longer for them to work compared to beta<sub>2</sub>-agonists but they have less side effects compared to the other bronchodilators. The most common side effects are the experience of dry mouth, dry cough, glaucoma and prostate problems.

## THEOPHYLLINES (METHYLXANTHINES)

The last class of bronchodilators is the theophyllines, these do also have a muscles relaxant effect and can reduce the swelling in the airways. The theophyllines are associated with the most side effects and should only be used when other bronchodilators do not work.

It may sometimes be useful to combine different bronchodilators since they work in different ways. This could be a better option than to increase the dosage of a single type.

## CORTICOSTEROIDS

Corticosteroids are a group of anti-inflammatory medications. They are used to reduce the inflammatory reaction within the lungs and to decrease the swelling of the bronchi.

Inhaled corticosteroids (ICS) are a treatment option for patients with severe COPD and for those who have a high frequency of exacerbations. ICS can also be recommended when long-term acting bronchodilators do not give sufficient relief from symptoms.

Long-term therapy with ICS should be combined with long-acting beta<sub>2</sub>-agonists to get the best effect since the beta<sub>2</sub>-agonists open up the airways and allow the steroids to reach their target.

Patients who are taking corticosteroids during a long period of time can often become more susceptible to infections. Corticosteroids can also be taken as a tablet or as an injection. Tablets are however not recommended as a long-term treatment due to the risk of developing osteoporosis or diabetes and they for that reason only recommended to be used when treating acute exacerbations. Detailed information regarding the dosage and administration should be discussed with a specialist.

## PHOSPHODIESTERASE<sub>4</sub>-INHIBITORS (PDE<sub>4</sub> INHIBITORS)

PDE<sub>4</sub> inhibitors are a rather new group of anti-inflammatory drugs that can be used to ease the exacerbations in patients with severe COPD.

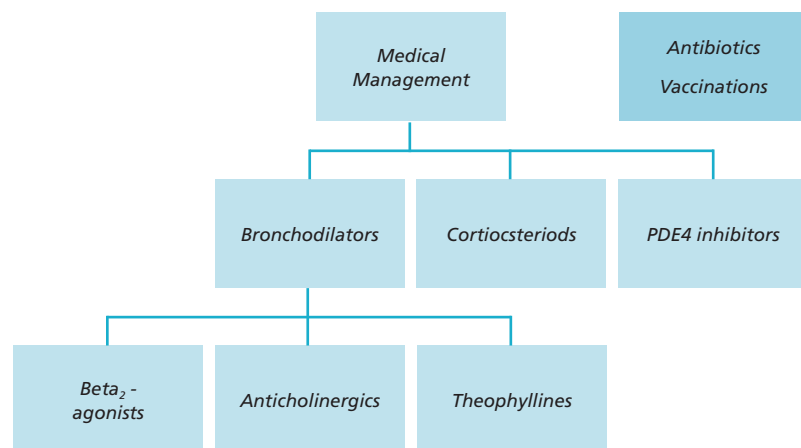
## VACCINATIONS

Patients suffering from COPD do often get infections due to their decreased health condition and for some who are suffering from severe COPD, a flu shot is recommended to reduce the risk from getting worse and more frequent exacerbations. Vaccinations against pneumonia are recommended to risk groups. Consult with your doctor if you think you need to be vaccinated.

## ANTIBIOTICS

Antibiotics can be prescribed when there is a bacterial infection, to treat serious exacerbations or to be given after an invasive procedure [8],[24].

## MEDICAL MANAGEMENT



## MANAGING EXACERBATIONS

Management of Exacerbations ([15],[24])

Treatments	Effect/Purpose
Short Acting Beta <sub>2</sub> + Short Acting anticholinergics	Treat severe breathlessness
Corticosteroids, tablets	Reduce the swelling
Antibiotics, if there is an indication of infection	Treat infection
Oxygen therapy	Increase the O <sub>2</sub> levels in the blood or decrease the CO <sub>2</sub> levels
Non-invasive ventilation	Breathing support or to compensate for an imbalance in the gas exchange
Ventilator	Mechanical ventilation

## LONG-TERM OXYGEN THERAPY

Long-term oxygen therapy may be prescribed when the disease is in a progressed stage (GOLD Stage III-IV) and the gas exchange between the lungs and the blood are affected causing an imbalance in the oxygen and carbon dioxide levels.

An arterial blood gas, ABG, test can provide information about the oxygen partial pressure (PaO<sub>2</sub>), the carbon dioxide partial pressure (PaCO<sub>2</sub>) and the pH and enables your doctor to determine how well the gas exchange is working.

A pulse oximeter can also be used to measure the levels of the saturated oxygen in the blood (SaO<sub>2</sub>), this test is simple and it is done by putting a clip on the finger. A normal value of saturated oxygen is 92-100 %

PaO <sub>2</sub> (Critical values)	SaO <sub>2</sub> (Critical values)
≤ 55mmHg at rest	≤ 90%
<50-60mmHg at rest with Cor pulmonale / polycythemia	< 90%
< 55mmHg during exercise or hypoxemia during sleep	< 90%

## CRITICAL OXYGEN CONCENTRATIONS

Indications on when oxygen therapy is given. The oxygen can be prescribed earlier than if the PaO<sub>2</sub> is below 7.3 kPa below 55mmHg if the patient is suffering from a cardiovascular comorbidity or during exacerbations

Once prescribed, the oxygen should be inhaled for at least 16 hours a day, and normally the closer to 24 hours the better since the body is unable to store oxygen. If the oxygen levels are only low during sleep or exercise, the oxygen therapy can be taken only during those occasions.

Long-term oxygen therapy has shown to have an effect on survival and it increases the exercise capacity [12]. It is very important to stick to the dosage prescribed since too much or too little oxygen could have severe side effects [15],[25],[26].

There are several types of delivery systems to choose from, depending on when you inhale the oxygen.



*The oxygen can be delivered either through a nasal cannula or a mask. A nasal cannula, delivers oxygen directly through the nose via a plastic tube with two nostril prongs. The tube is connected to an oxygen source.*



*Gas cylinder, liquid oxygen tank, mobile and stationary concentrators*

Different types of oxygen containers	Gas, liquid, oxygen concentration	Portable?
Cylinders/bottles	The cylinders contain compressed oxygen in gas form (stored under a high pressure (100 % O <sub>2</sub> )).	Yes, there are both large and small bottles available.
Liquid oxygen	Liquid oxygen takes up less space compared to oxygen in gas form, and they therefore last longer. To remain in liquid form the O <sub>2</sub> needs to be stored at -183 °C in a special container.	Yes, large and small tanks are available
Concentrators	A concentrator draws in the surrounding air, separates the oxygen from the other gases and filters out O <sub>2</sub> . The O <sub>2</sub> concentration obtained is approximately 90 %. It does not need to be refilled, runs on electricity	The most common concentrator is big and used at home, some of them allow a bottle to be filled.

## NON-INVASIVE VENTILATION

Non-invasive ventilation may be given either at the hospital to treat attacks of exacerbations or at home. It is used to adjust high carbon dioxide levels or to act as a breathing support when necessary. In contrast to a ventilator, non-invasive ventilation is given through a tight fitting mask and no intubation is needed.

There are two main types of ventilators, with different pressure modes: Continuous positive airway pressure, CPAP, and bilevel ventilators (BiPAP). In both of them, a positive airway pressure is applied, which gently presses air into the lungs, and thereby providing a pressure support. In the CPAP mode, one constant pressure is applied while the BiPAP ventilator has two different positive pressures, a higher upon inhalation and a lower during exhalation. A bilevel ventilator could either be spontaneous or timed depending on the condition of the patient.

In a timed mode the machine will initiate the breath on a preselected setting, if the machine is set on spontaneous mode, then the patient initiates the breath and the ventilator will only support this [27].

Non-invasive ventilation can sometimes be combined with oxygen therapy.

# SURGICAL TREATMENT

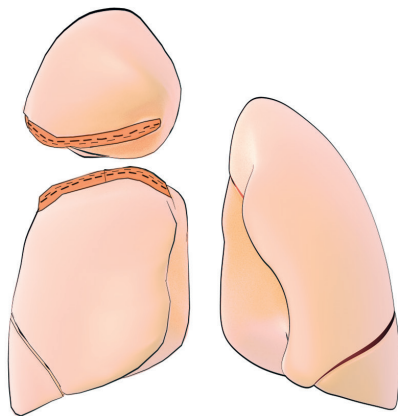
There is a small group of patients with emphysema who can be considered candidate for lung volume reduction surgery or lung transplantation. Surgical treatment may be an option in cases of severe or very severe emphysema, when other treatments do not work. The surgical treatments can be life changing but they are high-risk procedures.

## LUNG VOLUME REDUCTION SURGERY (LVRS)

In lung volume reduction surgery most commonly parts of, the upper lobes are removed. By removing parts of the diseased and over-inflated lobes, the surrounding lobes will be provided more space optimizing their capacity. Further, the pressure on the diaphragm will also be decreased enabling it to support breathing better.

Patient selection is essential for good outcomes.

LVRS in a carefully selected candidate has proven to increase lung capacity and improve the quality of life [28],[29].



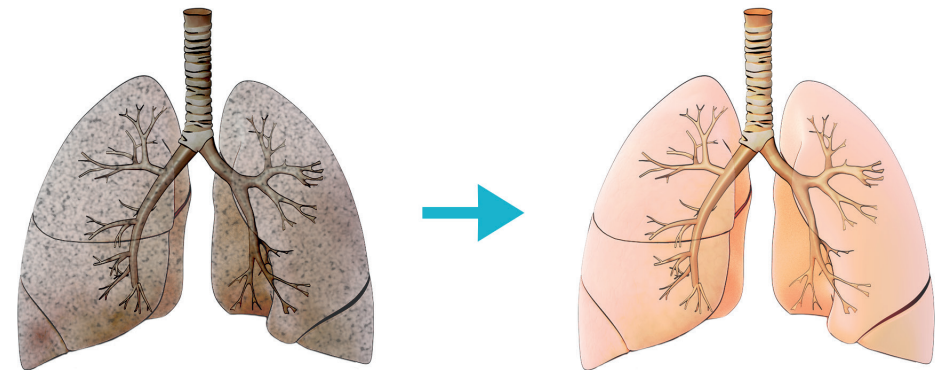
*During a LVRS, the upper lobes are being removed or reduced, staplers are used to seal the wound and to prevent air from leaking out.*

## LUNG TRANSPLANTATION

A small group of people who are suffering from very severe emphysema may be considered candidates for a lung transplant. The selection process for the procedure is extensive, and a long list of requirements needs to be fulfilled. Further, the organ shortage makes the waiting list long.

Both single and double transplantations are performed. Many patients who have undergone transplantation get an increased lung function, better exercise capacity and a higher quality of life.

The surgery is a high-risk procedure. Several post-operative complications are associated with lung transplantation. The recovery period is long and there is a risk that the body will reject the new lungs even if drugs are prescribed to prevent this [30].



# INTERVENTIONAL TREATMENTS

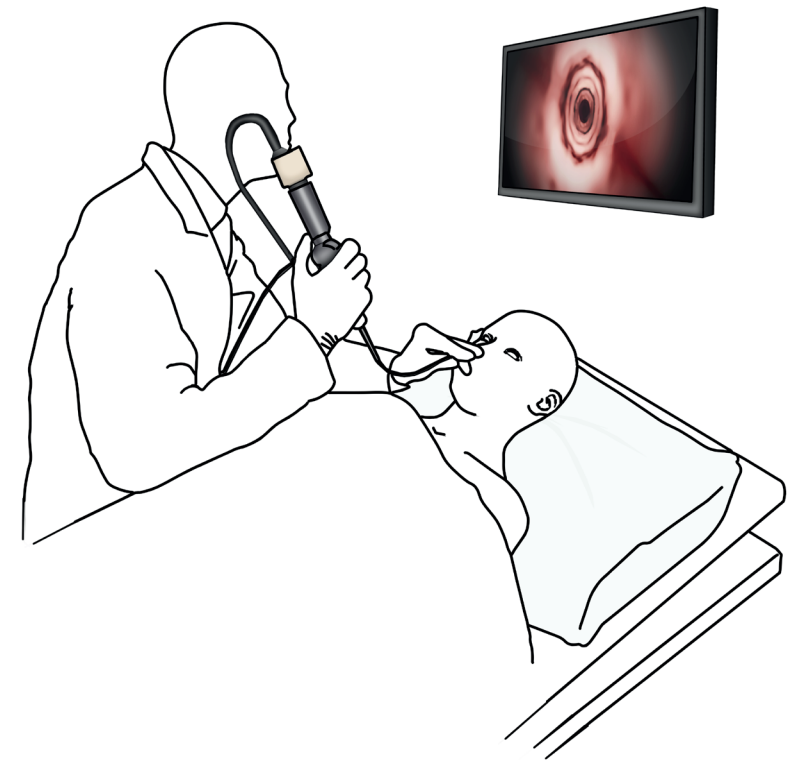
The previous chapter covered lung volume reduction surgery (LVRS), mentioning that LVRS has shown good results in improving lung capacity and quality of life. This was however the results from a small group of carefully selected patients with severe or very severe heterogeneous emphysema in the upper lobes [29]. New, less invasive alternatives to LVRS have been developed and evaluated in clinical trials during the last decade in order to meet the need of treating all lobes with a lower risk profile than e.g. LVRS. This is achieved by so called Bronchoscopic Lung Volume Reduction (BLVR). There are a couple of different BLVR techniques, which may be an option for people who are suffering from severe or very severe emphysema, who don't get sufficient help from medical treatments or pulmonary rehabilitation [31],[32].

For the last 10 years, a number of BLVR techniques have been approved for use. None of them require surgical removal of the target lobe, instead they all minimize the over-inflated lobe in a controlled way, either by blocking off air supply, mechanically reducing the lobe or by inducing an inflammatory reaction [31],[33].

Valves, coils, heated water vapor or polymeric sealants are placed or injected in the bronchial tree in the inlets to the diseased lobe. Many of those techniques are still being used on an experimental level and it is only one of the valves (EBV) that have been evaluated in large randomized controlled clinical trials.

## BRONCHOSCOPY

The valves, coils or liquids are being lodged or injected via a bronchoscope, which is a thin, flexible, long tube with a small camera attached at the end enabling a video to be displayed on a screen. The bronchoscope is inserted in the bronchial tree via the mouth or the nose. The valves or coils are being placed in the bronchus by a delivery catheter attached to the end of the bronchoscope.



*Bronchoscopy is a type of endoscopy where the airways are examined. The doctor can use this technique for diagnostic purposes or to perform bronchoscopic lung volume reduction.*



## REVERSIBLE - ONE-WAY VALVES

There are two different one-way valves used for BLVR: the endobronchial valve (EBV) and the intrabronchial valve (IBV).

These so-called one-way valves are placed in the bronchial tree in order to block the inlet of air to the targeted lobe. The EBV valve is constructed in a way to remain closed during inhalation, preventing new air from entering the lobe and then opening up during exhalation, allowing trapped air and fluid to escape out. The valves are delivered through a bronchoscope and lodged down in the branches of the bronchial tree. The EBV valve should be placed in a way so there is no leakage around the valve and so that a valve is placed in every inlet to the targeted lobe [33]. Normally, 2-5 valves are required to close off a lobe.

The desired outcome is to reduce the volume of the target lobe as much as possible.

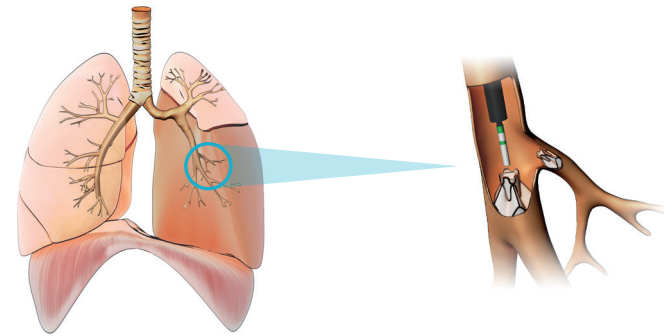


*The (EBV) valve is approximately 8 mm in diameter and 12 mm long. The framework of the valves is made of a metal called nitinol and it will adjust its size to the bronchus where it is placed. It has a silicone coating and a one-way valve protected by the nitinol frame.*



*The Intrabronchial valve has a shape of an umbrella, with a frame of nitinol and a polymer membrane.*

## EBV VALVE PROCEDURE



*The left lower lobe is enlarged and presses the diaphragm downwards.*

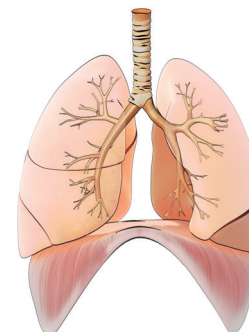
*Using a bronchoscope two valves are placed in the left lower lobe.*



*The valves allow air and mucus to escape out...*



*...while preventing air to re-enter the enlarged lobe.*



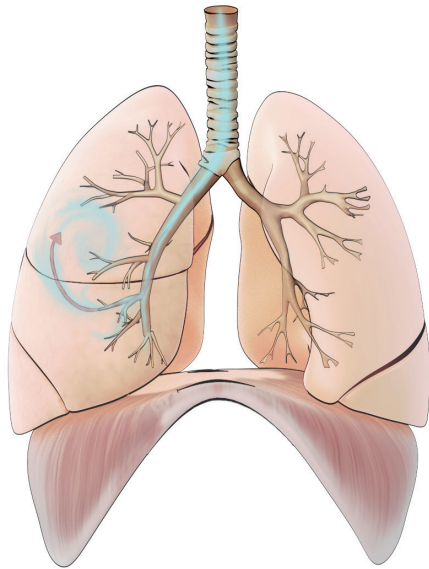
*As a result, the enlarged lobe becomes smaller and enables the upper lobe to expand. The pressure towards the diaphragm is also released making breathing easier.*

## COLLATERAL VENTILATION

When the disease has spread throughout the lungs, air can leak between the different lobes. This is a result of the air sacs being degraded to an extent where the different compartment in the lungs have become interconnected, the condition is referred to as collateral ventilation [34].

If air is leaking between the lobes the effect of using valves in one lobe may be lost.

To find out if the person has collateral ventilation or not, the doctor uses a bronchoscope, with a catheter and an inflatable balloon at the end. By isolating the lobe with the balloon, presence or absence of collateral ventilation can be recorded.



*When the fissures separating the lobes have been degraded, air can start to leak between the different lung compartments. This condition is referred to as collateral ventilation*

### Who is eligible for getting a valve?

Have a FEV1 between 15-45 % (predicted) and diagnosed with emphysema by a CT scan

Have a Residual Volume (RV) value over 180 % of the predicted value measured by a body plethysmograph

Have little or no collateral ventilation between the target lobe and the surrounding lobes

Have no allergies towards nickel, titanium or silicone

### THE MOST COMMON COMPLICATIONS ARE:

*Pneumothorax – a tear in the lung which causes air to leak into the sac surrounding the lung. This leak normally heals by itself after treatment with a chest drain.*

*Infection*

*Bleeding*

*Absence of benefit from treatment*

*Occasionally a valve can become dislodged and coughed out*

## SCIENTIFIC PUBLISHED EBV STUDIES

*The results of 2 randomized controlled clinical trials where one group of patients treated with optimal medical treatments and EBV valves was compared with another group that was only getting only optimal medical treatments, showed:*

*Statistical significant results of improved lung- and exercise capacity.*

*EBV showed to be safer than LVRS.*

*The studies showed that a group of patients with no collateral ventilation and heterogeneous emphysema emphysema and complete fissures responded much better to the treatment [35], [36].*

*A multicenter prospective study:*

*80 patients participated in a study where the catheter evaluation method was used to determine if the patients had collateral ventilation or not. The results from the study showed:*

*The diagnostic method is proven to be safe.*

*The diagnostic method of measuring collateral ventilation predicted correct outcome of treatment in 75% of the patients. In addition, the patients with no collateral ventilation showed a significant improvement in lung capacity (FEV<sub>1</sub>) [37].*

*In another study, where the long-term effects of the valve treatment were evaluated in regard to complete fissures showed:*

*83.3 % of patients getting valves who had complete fissures were still alive 10 years after the procedure, while only 24 % from those with no fissures had survived [38].*

*In a small study where the correlation between a post-operative atelectasis (volume reduction) after BLVR treatment and survival was evaluated showed:*

*All of the patients with atelectasis were alive 6 years after the procedure (5 out of 5) while 6 of 14 were alive in the group where atelectasis had not occurred [39].*

## IRREVERSIBLE ENDOBRONCHIAL LUNG VOLUME REDUCTION

The irreversible BLVR techniques include the use of heated water vapor and polymeric foam.

Coils can be removed under certain conditions, within a relatively short timeline of about 3-4 weeks after implantation.

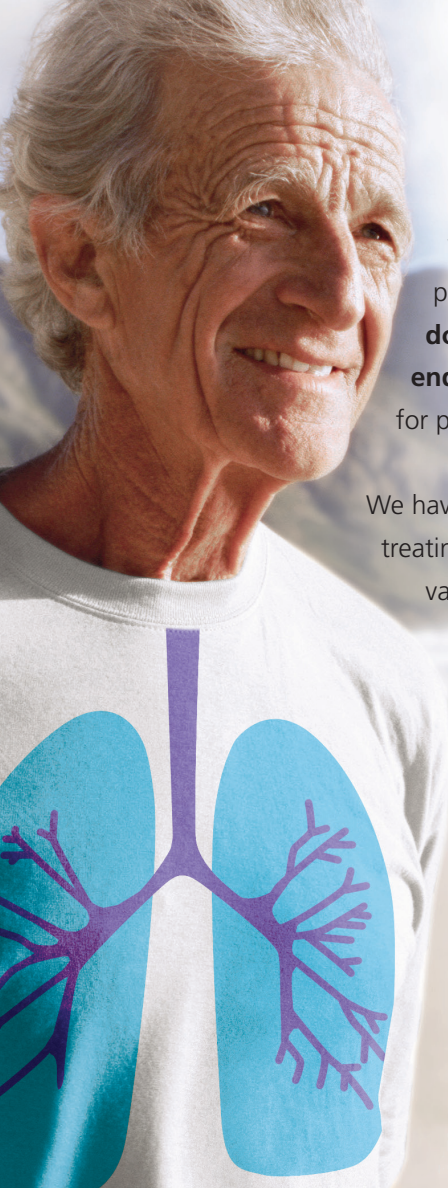
The lung volume reduction coil is made out of nitinol. Once in place in the lung tissue it takes the shape of a coil. It compresses the lung tissue in order to reduce the volume of the lobe, leaving room for the healthier lobes to function to their full capacity. This treatment method can both treat patients with or without collateral ventilation.



*The lung volume reduction coil in its original shape*

Vapor thermal ablation and polymeric lung volume reduction are both techniques where an inflammatory reaction is induced. Heated water vapor or polymeric foam is injected into the targeted lobe, causing an inflammatory response, which will lead to scarring and fibrosis and eventually a reduction of the targeted lung [31].

Note: These methods require further evaluation in clinical research studies. Therefore, they are not recommended to be used if not within a clinical trial.



# COPD

We at Pulmonx® are committed to provide information and training for **doctors and patients** on **endobronchial lung volume** reduction for patients with severe emphysema.

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# EMPHYSEMA

## COLOPHON

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### DESIGN AND ILLUSTRATIONS

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