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The History and Future Treatment of Emphysema

Emphysema Valves, Emphysema Coils and Volume Reduction Surgery

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Abstract

Emphysema is one component of the spectrum of Chronic Obstructive Pulmonary Disease (COPD) a condition that affects at least one million persons in the UK.

Emphysema is a lung tissue damage induced mainly by cigarette smoking. For that reason, the condition has been treated with nihilism by health care workers.

Breathlessness, weight loss and fatigue are the main manifestations. Up to recently only symptomatic treatment including inhaled bronchodilators, oxygen therapy, anxiolytic agents and opioids were provided to treat breathlessness.

However, over the past ten years, new interventional modalities of treatment have been introduced which revolutionised the outlook to this condition. This article looks back at the history of emphysema management and examines the exciting future of emphysema management.

The evening lecture on this subject was delivered by the author on Monday 19 October 2016 at the Create Centre – Bristol during the 2016 Annual General Meeting for the Bristol Medico-Historical Society.

Background

COPD is a progressive disease characterised by airflow obstruction. The obstruction is not fully reversible with current therapies. It is induced by cigarette smoking, exposure to other noxious gases include biomass fuel and by age. Rare congenital causes such as alpha 1 anti-trypsin deficiency can cause emphysema at a young age. COPD affects the lungs mainly but other organs including the cardiovascular system, the skeletal muscles and the weight bearing bones are also affected (GOLD Initiative 2016).

Nearly one million patients are affected by COPD in the UK, with an estimated another further two million undiagnosed.

COPD has two components; airway narrowing due to increase mucous gland and respiratory muscle constrictions and a damage to the small airways and alveolar spaces (parenchyma). The parenchymal component of COPD is emphysema.

The current management of COPD consists of two strands, the first is to treat symptoms, improve breathlessness and health-related quality of life- this normally happen by using bronchodilators. The second treatment strategies aim at reducing exacerbations, reduce the decline in lung function tests and improve survival. This strategy consists of smoking cessation, inhaled long acting bronchodilators and inhaled steroids ((GOLD Initiative 2016).

The difficulty with emphysema

Emphysema is defined as a destruction of lung tissue beyond respiratory bronchioles. Up to relatively recently, the gold standard method to make a diagnosis of emphysema has been considered to be a lung tissue biopsy. The histological appearance of emphysema is that of small airway destruction, widening of air-spaces and absence of alveolar tethering (figure 1).

The obvious difficulty in obtaining lung tissue sampling in vivo stood in the way of developing diagnostic and in evaluating therapeutic methods.

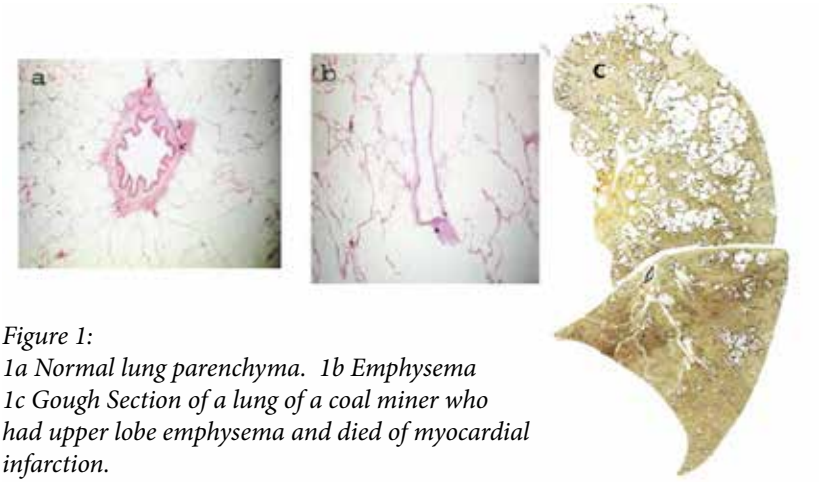


Figure 1:
1a Normal lung parenchyma. 1b Emphysema
1c Gough Section of a lung of a coal miner who had upper lobe emphysema and died of myocardial infarction.

The advent of high resolution CT scan has revolutionised our understanding of emphysema. CT scan has been able to accurately identify patterns of distribution of emphysema as well as its extent. Recognising upper lobe predominant disease, lower lobe disease homogenous emphysema and patchy emphysema (figure 2) enabled new thinking to develop methods to manage the disease interventionally. Most of the new work in describing the appearance of emphysema was made at the Bristol Royal Infirmary by Professor Paul Goddard (Goddard 1982).

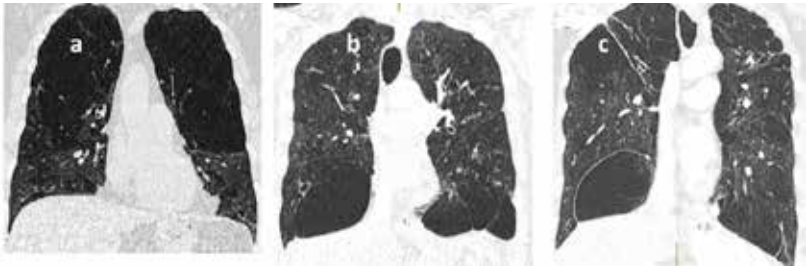


Figure 2: Coronal CT scan in 3 patients. –
Upper lobe emphysema (a),
lower lobe emphysema (b)
and patchy emphysema with bullous formation in the right lower lobe (c).

The mechanism of emphysema is not totally clear. It probably results from lung damage by excess proteolytic enzymes in smokers. These enzymes come from the granules in neutrophils. In most people anti-proteases (anti-trypsin for example) are present in sufficient quantities to capture and neutralise the released proteases. Therefore, most smokers do not develop emphysema. When the anti-proteases are insufficient in quantity or in quality, tissue damage is thought to result in emphysema (Abboud RT, et al).

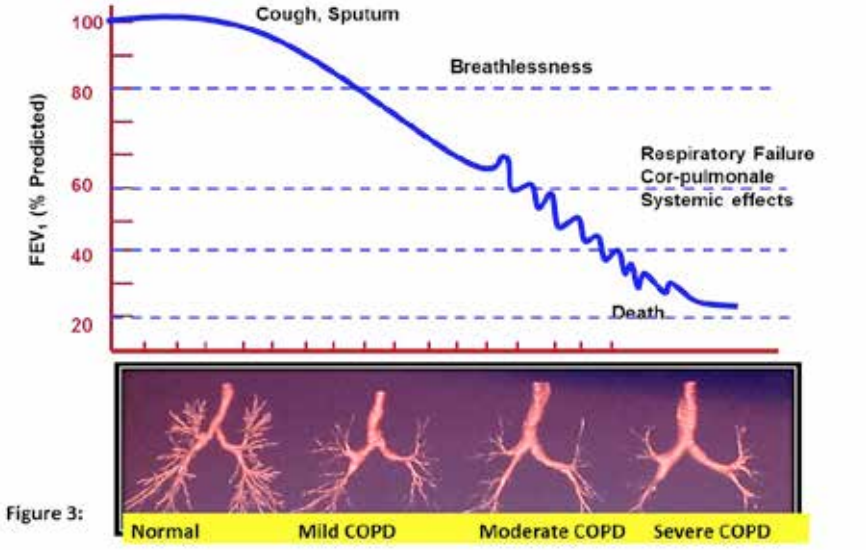


Figure 3:

Figure 3: Decline in lung function with age in smokers with emphysema. Below: bronchial tree casts of patients with different stages of COPD. Please note loss of peripheral and small airways even in the mild form of COPD. (Hogg J . European Respiratory Society (ERS) meeting – London 2016)

Recently, studies from bronchial casts in explanted lungs showed that emphysema occurred early in disease progress (Hogg J ERS 2016) (figure 3). These studies also revealed that, contrary to previous assumptions, the process of COPD and emphysema starts from the periphery of the lungs and gradually extend centrally as the disease process progresses. This is supported by studies on high resolution CT scans of the thorax (figure 4).

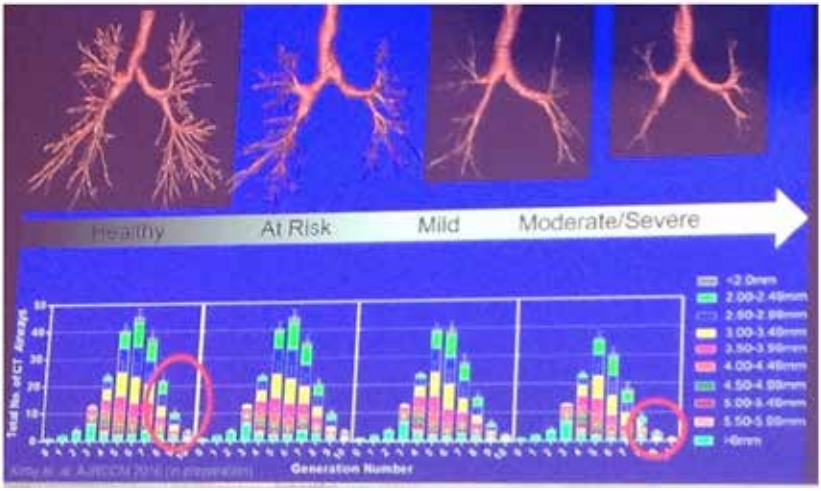


Figure 4: The bronchial casts of patients with emphysema – below this is a histogram showing the gradual loss of small airways on quantitative CT scans (red circles) Slide from Hogg J – ERS 2016

As emphysema advances, two pathological phenomena occur. The first is that the small airways get fewer in number (Diaz A 2010) and thinner and therefore become easier to either collapse and/or kink during expiration. This would account of the sudden reduction of flow seen on the appearance in flow-volume loop (figure 5).

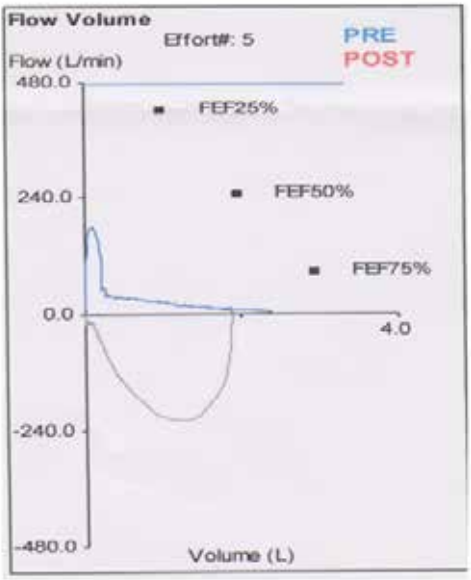


Figure 5:
Typical flow-volume loop for emphysema. Note the sudden reduction of flow accounted for by collapse of moderate size and small airways at forced expiration.

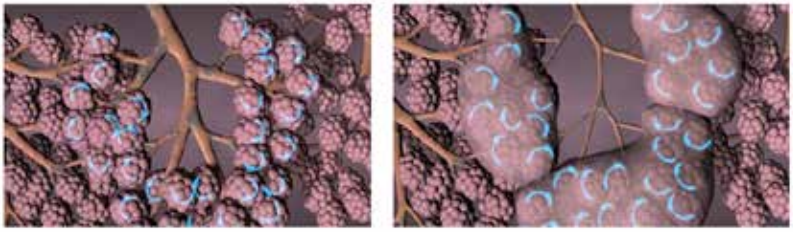


Figure 6: A schematic representation of (a) normal airways with intact number of small functioning airways and alveoli as well as good size airways and (b) emphysematous lung in which there is fusion of the alveoli causing air-trapping represented by the blue arrows and thinning of the airways. The thinning of the airways makes them prone to collapse during expiration.

The second is a fusion of alveoli forming large spaces, in which the air does not get a gas exchange, thus forming air trapping (figure 6).

Air trapping or hyperinflation is responsible for the classic appearance of patients with emphysema. It is responsible for the pursed lip breathing, the increase in anterior-posterior diameter of the chest wall (kyphosis) and probably in the failure to gain weight due to increase work of breathing in emphysema (figure 7).

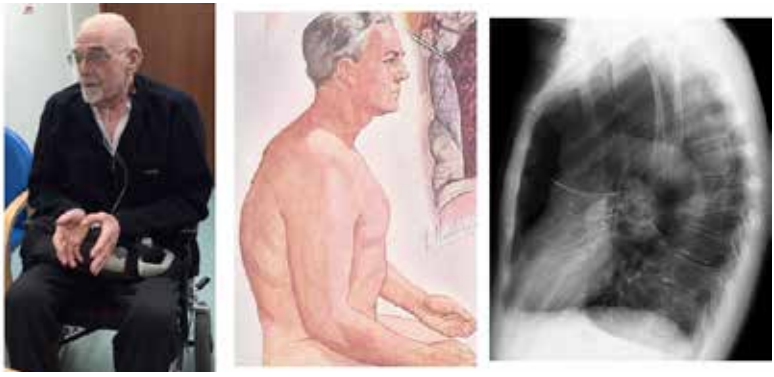


Figure 7: A patient with emphysema (a) – please note the reduced body mass index and the pursed lip breathing. (b) a schematic representation of the increase in anterior-posterior diameter (kyphosis) and (c) a lateral chest x ray of the patient confirming the kyphosis induced by lung hyper-inflation as well as low attenuation of the upper lung zones.

The epidemiology of emphysema:

As the diagnosis of emphysema previously needed biopsy and autopsy, epidemiological calculation had not been possible. However, a recent study examined the degree of the presence of emphysema and the extent of emphysema on quantitative CT scan of the chest (Schroeder 2013) in a large cohort of COPD patients enrolled in the COPD Gene Study. When examining the results of the study, emphysema , expressed as low attenuation area, was found to be highly prevalent when FEV1 reduced below 50% of predicted values and when FEV1/ FVC ratio was below 50% (figures 8 a and 8 b).

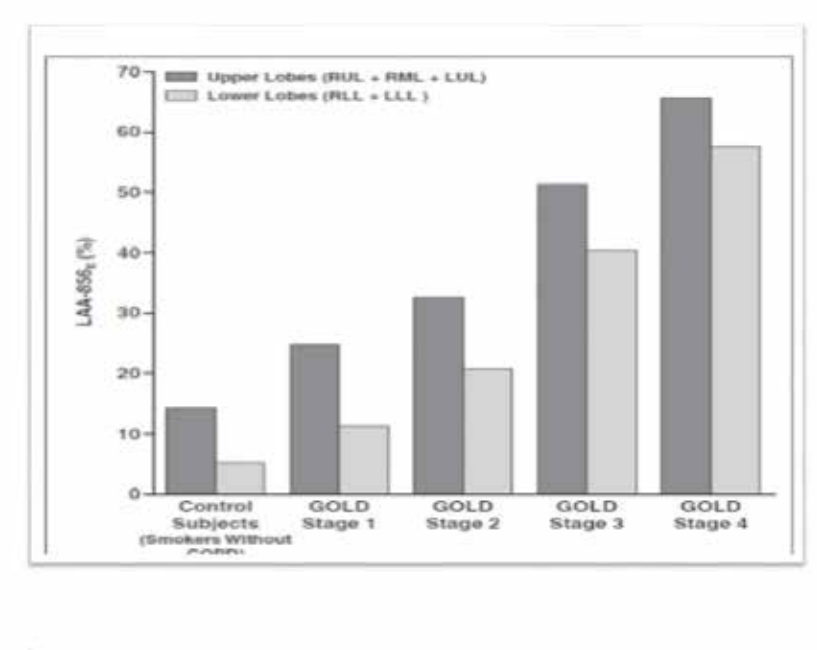


Figure 8a: Prevalence of emphysema expressed as Low Attenuation Area (LAA) on HRCT scans of patients with different GOLD stages depicting declining values of FEV1. Please note that when FEV1 declines below 60 % of predicted there more than 40% likelihood of patient having emphysema. From Schroeder 2013

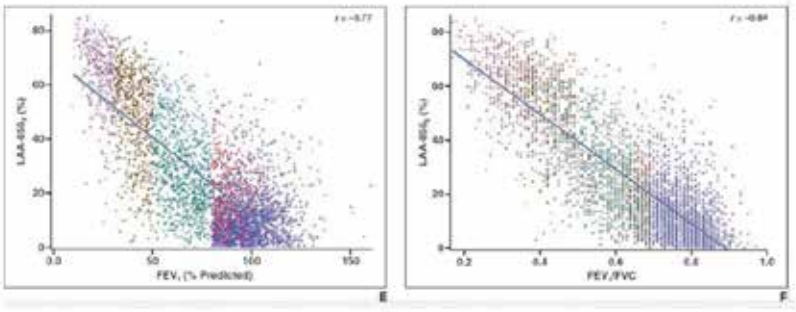


Figure 8b: The proportion of emphysema space on HRCT scan expressed as the Low Attenuation Area (LAA) Versus FEV1 (left) and the degree of Airflow obstruction expressed as FEV1/FVC ratio (right). This and figure 8a showed that not only the presence of emphysema but the extent of emphysema increases with reduced lung function (Schroeder 2013).

The lack of available pharmacological treatment for emphysema has resulted in the development of non-pharmacological methods in managing emphysema. These are mainly interventional procedures.

Interventional Management of emphysema:

Lung volume reduction surgery (LVRS):

In hyper-inflated lungs with severe air-trapping, removal of the most affected parts of the lungs was done on sound theoretical grounds. The intended benefits consisted of reducing dynamic hyper inflation and restoration of the mechanics of the chest wall and the diaphragm which are compromised because of hyper-expanded lungs.

The first attempt to remove parts of the lungs in patients with severe emphysema was undertaken by Brantigan in 1950 who operated on two distinctive pathologies: removal of bullous disease and removal of diffuse emphysematous part of the lung. The procedure was done through thoracotomy.

In 1957, the results of 89 patients were available (Brantigan 1957).

The study found clinical improvement in 75% of patients and in some it lasted for 5 years. The precise measurement of clinical improvement was not clear. No results in improvement in lung function tests were published. Mortality rate was 16%. Due to these shortcomings, Lung Volume Reduction Surgery (LVRS) did not take off as a credible procedure until the 1990s.

In 1993 the concept and the procedure of LVRS was revived by Cooper and colleagues who evaluated bilateral LVRS in bullous disease. They found a maximum benefit from removal of large bullae occupying more than one third of the lung and with reduced FEV1 below 50% of their expected values (Cooper 1995).

In 1998 and despite some positive results Healthcare Financing Administration (HFCA) halted the reimbursement of LVRS pending definitive evidence.

Several other studies reported advantages of LVRS. Criner (1999) reported improvement in lung function tests in LVRS for bullous emphysema compared to pulmonary rehabilitation. There was no difference in exercise capacity as assessed by the six-minute walk distance (6-MWD). Geddes 2000 on the other hand showed improvement in shuttle walk tests in LVRS of emphysema compared to best usual care.

High mortality rate from LVRS was reported in a study by Hillerdal in 2005 despite improvement in quality of life in those who survived the treatment.

The ultimate answer to the place of lung volume reduction surgery came from the National Emphysema Therapy Trial (NETT). NETT was planned as a prospective multicentre clinical trial comparing usual care in emphysema with volume reduction surgery. The recruitment period lasted from 1998 to 2002. A total of 1218 patients were included with 1:1 randomisation. The main outcome was exercise capacity using a maximum workload on cycle ergometer. Survival advantage was the second main outcome. The duration of follow-up was 5 years.

The study found that in all participants LVRS offered a small

improvement in exercise capacity over medical treatment. There was no survival advantage over usual medical care. However, further sub-analysis demonstrated that patients with prior good exercise capacity and non-upper lobe emphysema did not have a functional gain and suffered highest mortality rate. This contrasts with patients with upper lobe disease and poor exercise tolerance who gained the best survival advantage (figure 9).

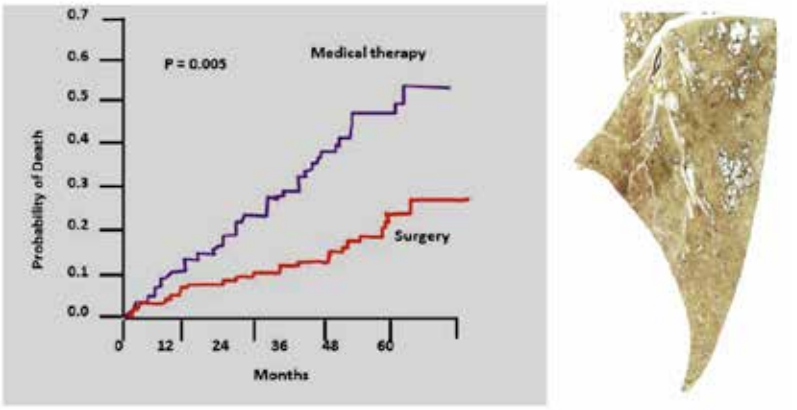


Figure 9: Favourable survival curve in surgically treated patients in a sub-group of patients in the NETT trial – those with upper lobe emphysema and poor exercise tolerance.

The 30-day mortality rate in the LVRS group was tenfold greater than those in the medical group (2.2 and 0.2 respectively). The 90-day mortality rate in the surgical group was four times greater than in the medical group (5.2 and 1.2 respectively).

The morbidity rate of LVRS was also considerable leaving 28% of patients in nursing homes or being re-hospitalised within 30 days of the procedure. Despite all these, NETT has not increased enthusiasm in utilising LVRS as a method of treatment of emphysema.

Separately to NETT, centres with high volume of LVRS published more upbeat results compared to NETT. In a retrospective analysis by Weder et al (Weder 2009) found persistent improvement in efficacy of staged bilateral video-assisted thoracoscopy treatment in 225 patients

with heterogeneous and homogeneous emphysema. Improvement of FEV1 and 6 MWD was seen in equal measures in the two study groups. The improvement lasted for 36 months. Lung transplant was obviated in 64% and 73% of homogeneous and heterogeneous emphysema respectively after 5 years of the study (figure 10).

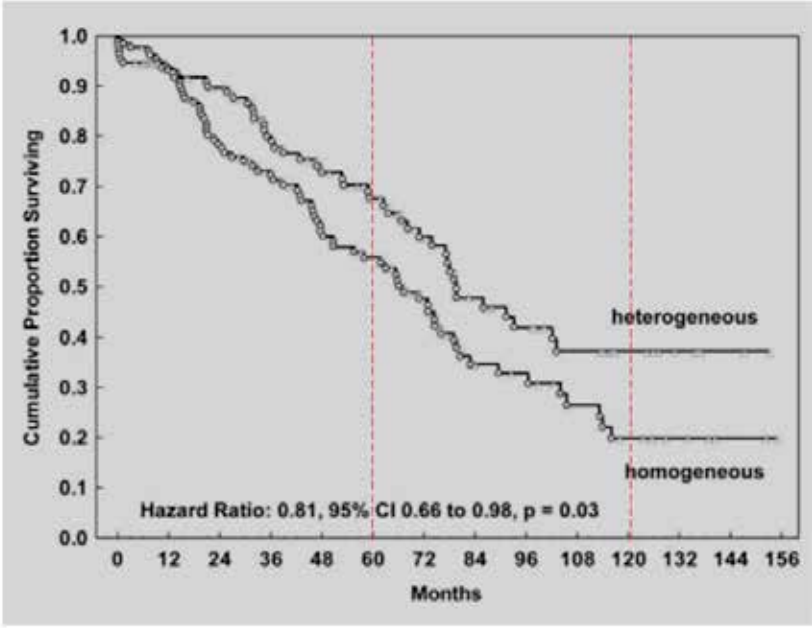


Figure 10: Favourable survival curve without transplant in surgically treated patients with heterogeneous and homogeneous emphysema. Weder (2009). Note the high survival rate at 5 and 10 years, in particular for patients with heterogeneous emphysema

One-month mortality rate was 2.3% in both groups.

Despite this study, LVRS remained an unattractive method of managing emphysema patients except in a small selected group. The popularity of LVRS remained low among thoracic surgeons as well as respiratory physicians (McNaulty 2014).

More recently, the role of LVRS has witnessed resurgence. This is mainly owed to the introduction of endo-bronchial volume reduction therapies. The introduction of the multi-disciplinary team meetings in which thoracic surgeons take part raised the interest in thoracic surgery as a method of LVRS and management of bullous disease. Many thoracic surgeons have taken a fresh look at the results of the NETT trial. This is owing to several reasons:

- Developments of new stapling methods with less possibility of air-leak.
- Reliance on differential perfusion scores between the target lobe and the adjacent lobe.
- Development of risk scores, with high risk includes composite factors: TLco < 20%, FEV1 <20%, pulmonary artery pressure of over 45 mm Hg, and co-morbid conditions.

For all these reasons, a prospective clinical trial (CELEB) is currently underway. The trial compares various subjective and objective outcome measures of LVRS versus endo-bronchial valves insertion in emphysema including lower lobe disease.

Endo-bronchial management of emphysema:

Endo-bronchial management of emphysema is a minimally invasive method of volume reduction. Several techniques have been developed and investigated over the past ten years. These methods are outlined below.

Tables 1a and 1b show broadly the criteria for referral and acceptance for volume reduction therapies.

(FEV_1) < 50% of expected values
Stopped smoking Undergone pulmonary rehabilitation programme
Modified MRC Breathlessness Score >2 COPD assessment Test score (CAT score) > 15
No major co-morbid conditions

Table 1 a

Has emphysema on chest CT scan
High air trapping – residual volume over 170% predicted
Rule out 'uncontrolled pulmonary hypertension' (degree depends on the proposed procedure valves, coils or surgery)
No major co-morbid conditions

Table 1 b

Table 1: Criteria for referral (Table 1 a) and criteria for acceptance (Table 1b) for volume reduction therapies

Endo-bronchial valves:

Endo-bronchial valves are one-way devices which, once in place, prevent air from entering while allowing the air out of the lobe. The aim is to collapse the target lobe and reduce its pathological influence on the better lobes in the lungs. The procedure effectively mimics LVRS but without removal part of the lungs. Unlike LVRS it is employed effectively in upper lobes and non-upper lobes.

Two valves are currently used- the zephyr valve (Pulmonx, Redwood City, California, USA) and the Spiration valve – Olympus Inc (figure 11).

Figure 11:
The Zephyr valve (Pulmonx) (A) and the Spiration (Olympus) valve B

Most of the evidence has come from the Zephyr valves, although large studies are now either underway or have been published in abstract forms. The first generation of the zephyr endo-bronchial valves was the Emphasis valve – (Emphasis-Redwood City, California). The valve consisted of three parts – the duck bell valve, the retainer and the seal (figure 12).

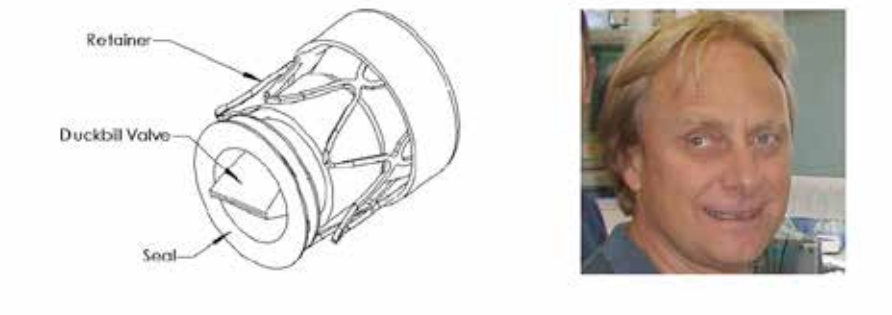


Figure 12: The emphasis valve (the first generation of zephyr valve). The valve consists of a retainer made of a nitinol cage, a seal made of silicon and the valve itself (duckbell) valve made of Silicon. The first animal and clinical work was published by Dr Gregory Snell (right) – (Snell 2003).

The valve was difficult to use and the procedure needed two operators, general anaesthesia, a rigid bronchoscope as well as a flexible bronchoscope. The work on these valves was first described by Snell and colleagues (Snell 2003). Their first step was to examine in vivo the efficacy of these valves on three sheep lungs aiming to familiarise themselves with valve insertion technique and with the post insertion effect. A post mortem removal of the lungs after valve insertion showed a collapse in the treated lobe in two out of three sheep. No intra-operative problems were encountered.

The valves were then inserted in ten patients with severe emphysema. The main aim of the pilot was to investigate safety and tolerability of the procedure. The average operative duration was two hours and forty-eight minutes. The procedure was found to be safe. No changes were seen in lung function or on CT scan in many patients. However, gas transfer (TLco) values had improved and lobar perfusion and ventilation diminished.

Figure 13: The 3 sizes of the Zypher valve (above). The valves are the size of peanuts. The sizes are made to fit several size bronchi. Below an animation of the valve opening during expiration (A) to allow air and secretion to leave the lobe and closes during inspiration (B).

The introduction of the Zephyr (the author used this valve) (figure 13) and the Spiration valves (the author has no experience in introducing) has simplified the intra-operative techniques. The procedure can be done by one or two persons under sedation through a fibreoptic bronchoscope (figure 14). The average time for valve insertion is thirty minutes although a pre-measurement of collateral ventilation using a follow catheter (see below) might take similar time.

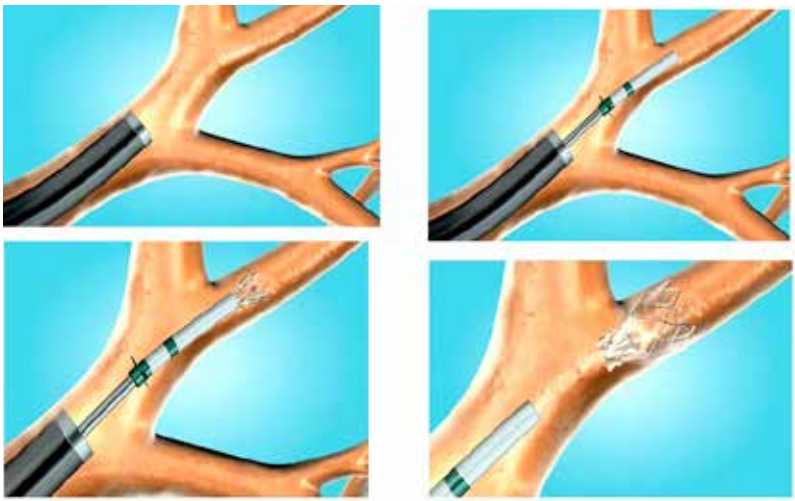


Figure 14: Image capture of insertion of an endo-bronchial valve in the apical segment of the left upper lobe.

The procedure is well tolerated and is reversible and valve removal is relatively simple in cases of complications or misplacement (figure 15).

A good outcome of endo-bronchial valve insertion hinges on the resultant lobe occlusion and subsequent partial or total collapse. When this happened, studies demonstrated significant improvement in various subjective and objective outcome measures including survival.

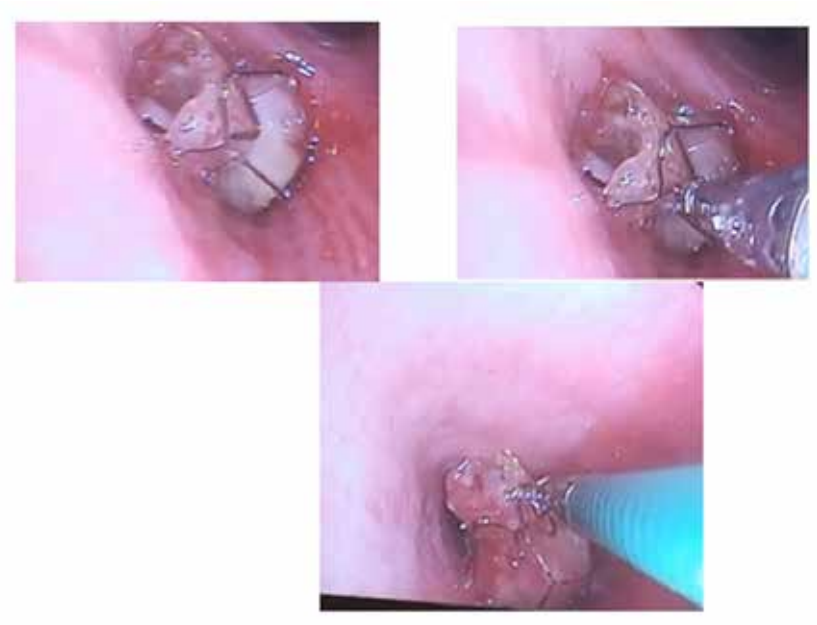
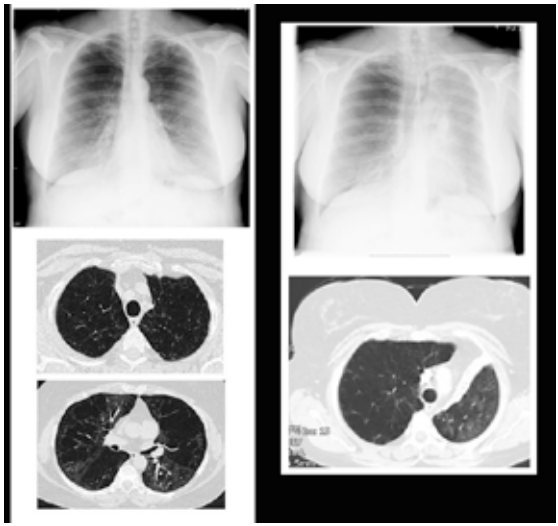


Figure 15: Removal of a misplaces endo-bronchial valve.

The procedure is illustrated in figure 14. A successful effect is illustrated in figure 16.

Figure 16:

The left panel shows a chest X ray and two CT slices before insertion and the right panel is of an X ray and a CT scan after insertion of endo-bronchial valves in a 71 year old lady.



The effectiveness of the Zephyr valves was sought in a large prospective clinical trial (the VENT study Scuirba 2011). This was a six months follow-up study conducted in the USA (321 patients) and in Europe (171 patients). The study was a 2:1 randomised study comparing valve insertion to usual care. The study was not blinded. The ultimate purpose of the study was to gain the approval of the US Food and Drug Administration (FDA) so that the practice may be rolled out in the US. The US arm and the European arm were reported separately.

The US arm of the study yielded disappointing results. Only a modest in-between group improvement in FEV1 of 6.8% was achieved. The improvement in 6-minute walk distance (6-MWD) was smaller at 5.8% in the group receiving EBV compared to the control group. The changes in FEV1 and 6-MWD were well-below the minimal clinically improvement difference (MCID). However, two subgroup analyses were undertaken to try and identify the best responders. The study found that high emphysema heterogeneity between the target and the adjacent lobes (in the US but not in the European study) and the degree of completeness of the inter-lobar fissure (in both studies) has resulted in a more favourable and meaningful improvement in FEV1, and St George's Respiratory Questionnaire score (SGRQ) in the group who underwent endo-bronchial valve insertion compared to the control group (figure 17).

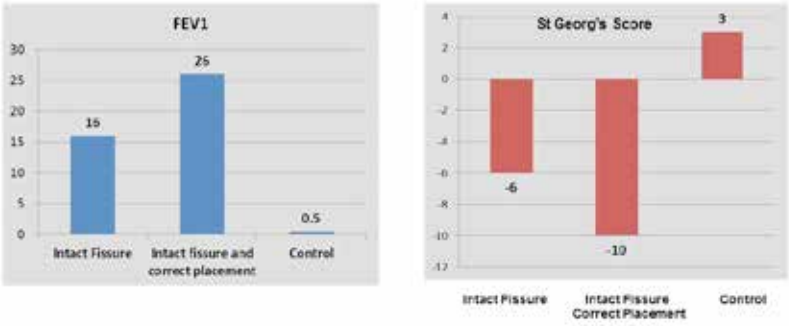


Figure 17: The results of the European Cohort of the VENT study. Please note a significant and meaningful improvement in FEV1 and SGRQ after insertion valves when the inter-lobar fissure is intact and after correct insertion resulting in lobe atelectasis. (Herth 2012)

As a result, selection of best responders from EBV has undergone a significant change. To put it simply, the likelihood of success and the benefit from the treatment are greater in the absence of collateral ventilation and with the correct placement of endo-bronchial valves. The selection for volume reduction therapies needs a minimum set of investigations. These are:

- high resolution computed tomography (HRCT) of the thorax,
- detailed lung function tests which include spirometry, lung volume measurement and measurement of gas transfer values,
- echocardiogram,
- 6-minute walk distance (6MWD)
- assessment of quality of life by either St George's questionnaire or COPD assessment test (CAT) score.

The role of lung isotope scanning by ventilation or perfusion is currently debatable but in the author's institute, a Single Photon Emission Computed Tomography (SPECT) CT scan is obtained in almost all patients (figure 18).

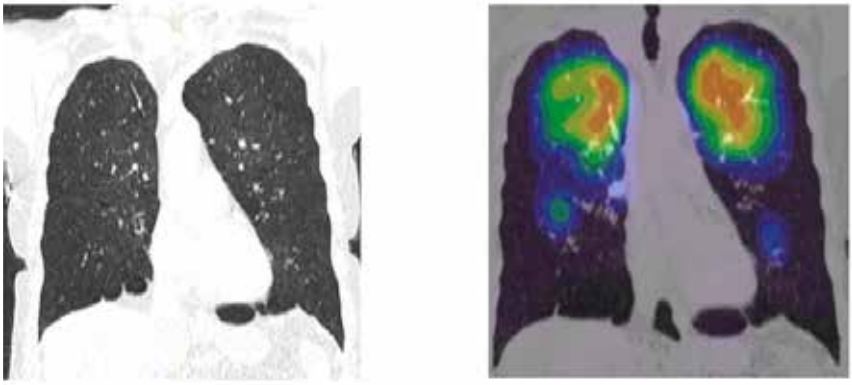


Figure 18: A single photon emission computed tomography (SPECT) in a 61 year old patient with lower lobe emphysema and heterozygote alpha1 anti-trypsin deficiency. Note that the CT scan (left) under-estimates the differential uptake illustrated on the SPECT scan.

Intact inter-lobar fissures:

The intactness of inter-lobar fissure can be assessed on 3 D HRCT scan. Eyeballing the fissure has, until recently, been the standard method. Studies showed that eye-balling of the fissure had a good inter-observer agreement at a high degree (over 80%) and at low degree (below 60%) of fissure intactness. Greater differences between assessors was observed, however, when the intactness of the fissure ranged between 60-80% (Koenigham-Santos 2012).

Patients with intact fissures who were treated in the VENT study (Scuirba 2010) in both arms achieved good improvement in FEV1, SGRQ and 6 MWD. A retrospective analysis has shown, that in this group, a continuous improvement in FEV1 and significantly high survival after five years of valve insertion.

The degree of fissure intactness necessary to achieve post valve atelectasis has also been investigated. de Oliviera (2016) found that 75% or over was associated with atelectasis in 12/14 (85%). In contrast, fissure completeness of < 75% was associated with atelectasis in 1/9 (11%) of patients. Similar predictive values were reported in a study by Schumann et al (2015).

However, the use of fissure completeness alone by visualising the CT scan proved to show sub-optimal response in a single centre prospective sham blinded valve-sham controlled study (Davey 2015). In this study, a modest albeit significant response to valve insertion was achieved after three months of insertion of valve compared with the sham control arm. Chartis was assessed but not used in the entry criteria. None of the four patients who were later found to have CV positive pattern experienced lung atelectasis of showed increase in FEV1following valve insertion. However, the procedure in this study had a low atelectasis rate with only 50% of treated patients achieved complete atelectasis.

The use of both; fissure intactness and Chartis catheter as methods to rule out collateral ventilations was associated with impressive results in another single centre open label study (Klooster 2015). Using both methods have been the policy in the author's unit from the outset of

setting up this service.

More recently, automated methods of calculating fissure intactness have been developed and evaluated. The Stratx software (Pulmonx) is one example (figure 19).

Figure 19: A quantitative CT scan using StratX software. The patient has highly heterogeneous emphysema and fissure completeness on the left side. A high degree of emphysema is observed in the right upper lobe (84% of the lobe) and in the left upper lobe (83%). The lowest degree of destruction is seen in the left lower lobe (43%). The left oblique fissure is 100% intact. - the right oblique fissure is 66% intact. This patient is likely to respond insertion of endo-bronchial valves in the left upper lobe without the need to use Chartis flow catheter measurement.

Using this software, HRCT scans of previous clinical trials were analysed (Koster 2016). The degree of post-procedure atelectasis was taken as the main arbiter of the parameters obtained by this software. The study found that over 95% fissure completeness predicts therapeutic success in 82% of cases. This would suggest that valves could be inserted based on high fissure completeness seen on QCT scans alone with no need to using Chartis catheter.

Assessment of collateral ventilation using endo-bronchial flow catheter (ChartisR):

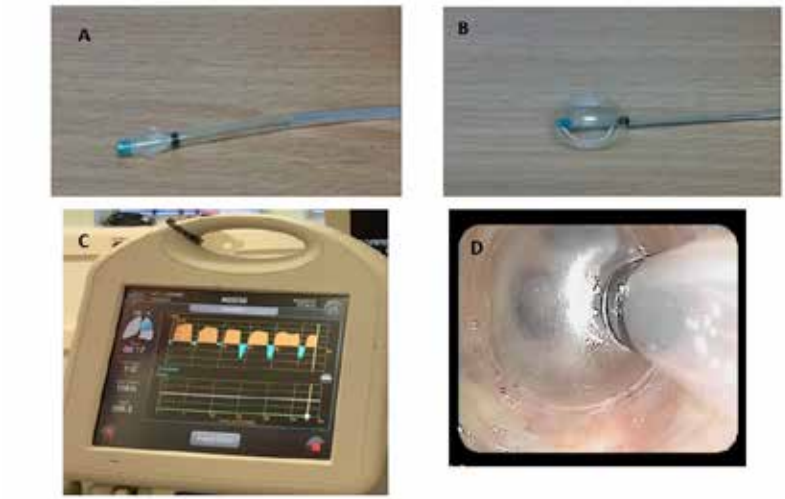


Figure 20: The Chartis catheter deflated (A) and inflated (B), the Chartis console [c] and the Balloon catheter inflated in the left upper lobe.

The ChartisR system [Pulmonx – Redwood City- California USA) consists of a balloon catheter attached to a sensor based in a console (figure 20). The catheter is inserted through the working channel of the bronchoscope and inflated to occlude the orifice of the target lobe.

A standard Chartis graph contains information displayed as a time-flow graph. Patterns of Chartis graphs are illustrated in figure 21.

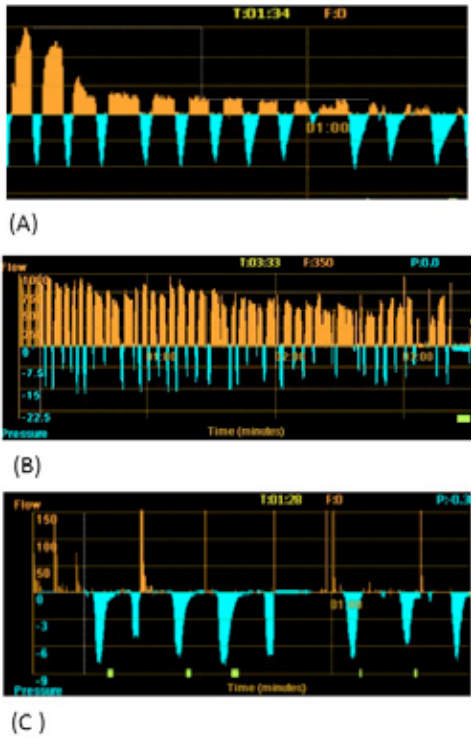


Figure 21: Three Chartis graphs from 3 patients. A: collateral ventilation (CV) negative pattern. Please note the decline in flow (orange) with time. The blue graphs help to identify a proper sealing of the catheter. CV negative pattern predicts post-valve atelectasis. B: this is a CV positive pattern which predicts no response to valve insertion. Pattern C: is a no flow pattern in a highly destructed lobe and bullous formation.

A collateral ventilation (CV) negative graph shows typically a gradual reduction in the flow to the point of becoming invisible after few minutes of lobe occlusion. CV negative pattern would be an indication of high success rate after proper valve insertion. A CV positive pattern would show no reduction in flow over time after occluding the main bronchus of the target lobe. Valves inserted in patients with this type resulted of high degree of failure. Other patterns of Chartis graphs have been described the sudden loss of flow, the low amplitude pattern and the no-flow graph. Examples of each of these graphs are seen in figure 21. The sudden loss of flow is attributed to collapse in the airways and alveoli. The no-flow pattern is often seen in lobes with a large degree of destruction or in bullous disease. It has been suggested that, if either of these patterns are seen, relying on the fissure completeness on the HRCT appearance would be the way to decide to insert the valves or not.

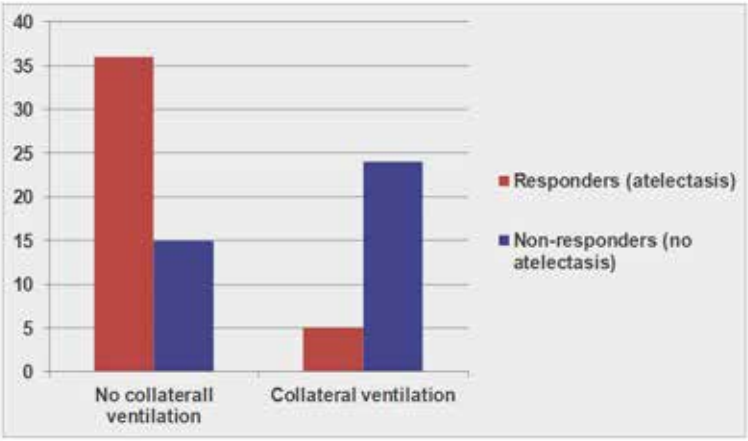


Figure 22: Rate of response according to the flow pattern- Herth 2013.

The low plateau flow pattern is thought to be a marker of small collateral ventilation with valve insertion likely to be unsuccessful.

The usefulness of the Chartis was reported in a study by Herth and colleagues (Herth 2013). In this study, a 350 ml volume reduction was regarded the clinically important volume loss after valve insertion. The study found that volume reduction occurred in most patients in whom the Chartis recordings showed CV negative pattern. In contrast, when the pattern was shown to be CV positive post valve volume reduction occurred in the minority of patients (figure 22).

Differences in the likelihood of lobes being CV negative, and therefore may predicts response to valve insertion, varies differ lung lobes. The likelihood of CV negative pattern has been seen more frequently in the left upper lobe and the left lower lobe, followed by the right middle lobe. The least likely lobe to show CV negative pattern is the right upper lobe. The fissures between right middle lobe and right upper lobes are often breached and the CV pattern in the right middle lobe is highly likely to be CV positive pattern (Herzog 2016).

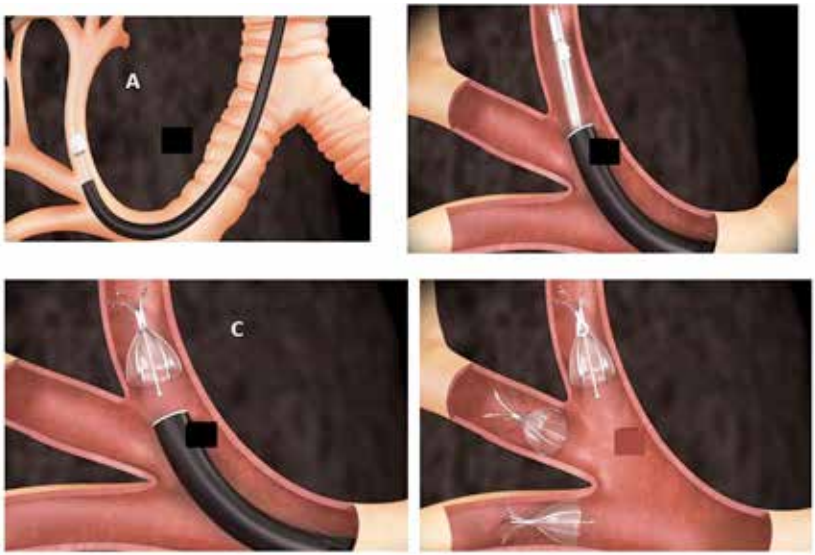


Figure 23: Insertion of Spiration valve. A. A balloon catheter measures the diameter of the airway. B. The valves deployed into the target bronchus and C: it is secure in place by . The stent mechanism and by 5 anchors. All bronchi leading to the target lobe are occluded (D).

Evidence for Spiration Intra-bronchial valves (figure 23):

The Spiration Intra Bronchial valve (IBV) (Olympus) is an umbrella like valve. The valve is inserted via a fibre optic bronchoscope. Three sizes of the valve are used. Lack of collateral ventilation relies on evidence from HRCT.

Two prospective studies comparing valve insertion with standard care are ongoing. The SVS Reach trial aimed at recruiting 100 patients in a single centre in China with 2:1 randomisation with usual care. Change in FEV1 at 6 months point is the main point of the study. The study was reported in an abstract to the proceedings of the European Respiratory Society Conference in London – September 2016 (Shiyue Li – 5 September 2016).

The study found significant and consistent improvement in FEV1, 6-MWD, Breathlessness score at the mMRC questionnaire and

improvement in quality of life as assessed by SGRQ and the COPD assessment test (CAT) score. A larger multicentre study (EMPROVE) with similar design to the SVS study is currently recruiting in the US and Canada. The study is ambitiously aims at recruiting 270 patients in 37 centres.

Complications of endo-bronchial valves (EBV) insertion:

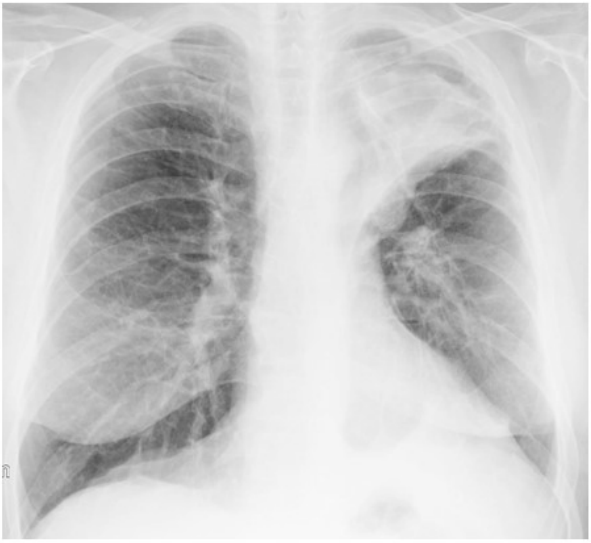


Figure 24: Pneumonic illness in the left upper lobe two months after insertion of endo-bronchial valves in the left upper lobe.

Several side effects and complications are expected after insertion of EBV.

- **Infections and COPD exacerbations:** Temporary increase in COPD exacerbation has been reported in up to 20% of the cases. These may represent true exacerbations or a reaction to the insertion of foreign body. Prevention of exacerbations is attempted by prescribing prednisolone and/or antibiotics prior to and after the procedure. However, there are no studies to support this practice.
- **Chronic cough.** This is a symptom that occur in approximately 15% of patients. This is probably due to reaction to the presence of the valves in the bronchi. In the author's unit, cough necessitated removal of the valves in 2/88 patients.

- **Pneumonia** distal to the valve is seen in 3.2% of patients (figure 24). This should be managed in the usual way. Occasionally abscess formation in the emphysema spaces is seen.
- **Temporary haemoptysis** is also encountered and often does not require any treatment. In the authors unit, anti-coagulation and clopidogril (but not aspirin) are withheld 7-10 day prior to valve insertion and re-started 72 hours after the procedure.
- **Pneumothorax (figure 25)** is one of the most serious complications of EBV.

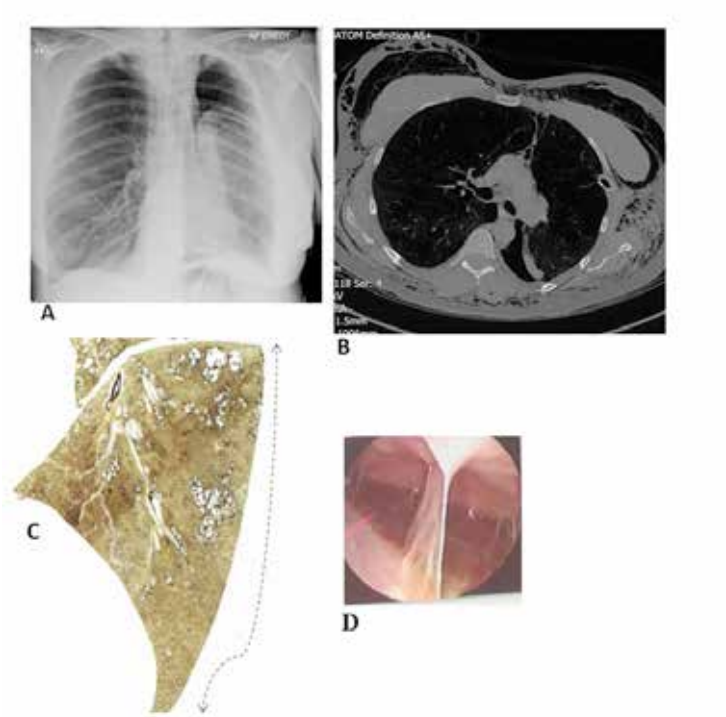


Figure 25: Pneumothorax after insertion of endo-bronchial valve in the left upper lobe. A. A chest X ray showing a pneumothorax in the left upper zone not responding to an inter-costal drain. B. A CT scan of the same patients 48 hour after showing Sub-cutaneous emphysema (the valves are in situ). C. A schematic representation of the mechanism of pneumothorax as a marker of expansion injury D: Adhesion between the visceral and parietal pleura which is probably another mechanism of pneumothorax.

insertion. The mechanism is thought to be a rapid expansion of the lobe adjacent to the target lobe after the collapse of the treated lobe. In some patients, adhesions were observed on video assisted thoracoscopy between the visceral and parietal pleura. Tearing of these adhesions upon expansion of the lobe has also been proposed as a mechanism of pneumothorax.

Pneumothorax happens in approximately 20-25% of patients. It almost always occurs in patients with complete fissure and a successful collapse of the target lobe. Over 90% of pneumothoraces occur within 72 hours. In the author centre all pneumothoraces occurred within few hours from valve insertion. For that reason, a hospitalisation for 3-5 days and a daily chest X ray after valve insertion is recommended. A retrospective observation by Gompelmann and colleagues (2014) found that pneumothorax predicts a favourable late response to valve insertion.

The management of pneumothorax depends on its size, its clinical impact and the presence of broncho-pleural fistula. Observation is sufficient for patient with a stable small pneumothorax with little symptoms and normal oxygen.

A chest drain is inserted when the pneumothorax is severe or persistent. Less frequently, broncho-pleural fistula with continuous large leak may occur. In this group, surgical management of pneumothorax may be indicated. Removal of one or all valve may be necessary to stop pneumothorax in some patients.

Reinsertion of endo-bronchial valves after pneumothorax is possible and does not necessarily result in recurring pneumothorax. Some physicians however chose not re-insert valves especially when the initial pneumothorax is severe.

Prevention of post-valve pneumothorax has been attempted by changing style of activities after valve insertion. One study demonstrated that avoiding cough by providing cough linctus's and reducing physical activities for few days has resulted in reduction in the rate of pneumothorax. The rate of thrombo-embolic events did not increase (Huebner 2015).

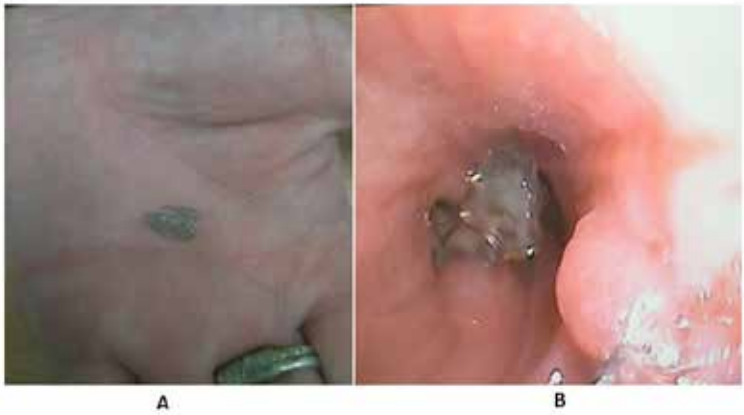


Figure 26: (A) Expectoration of a valve in a 54 year old patient. (B) Valve incompetence due to formation of granulation tissue in a 71 year old patient.

- **Valve migration and dislodgement**: Valves could be displaced after insertion leaving a gap and air leak that obviates the desired collapse of the target lobe. In the minority of patients the valves is dislodged and coughed up (figure 26). The reason for that is thought to be either incorrect insertion of the valves or choosing a smaller size valve. The latter can easily occur because bronchial oedema occurs during the Chartis procedure or during bronchoscopy. Oedema can reduce the calibre of the airways when measured. This may result in choosing a smaller valve size although in some patients, valve migration can occur for no obvious reason. Migrated and dislodged valves can be removed, and new valves are inserted. The procedure is technically easy and can result in good response.
- **Formation of granulation tissue**: Valves are foreign partly metallic bodies. Formation of benign granulation in the bronchial mucosa is common although the exact rate is not clear. Granulation is observed during bronchoscopy. Granulation tissue may be responsible of haemoptysis or loss of efficacy of inserted valves by changing the architecture of the bronchi (Figure 26). Valve removal and re-insertion after few weeks can restore the function of the valves.

- **Death** can occur after endo-bronchial valves in up to 3%. Patients needing endo-bronchial valves are challenging. They have severe emphysema and often have other co-morbid conditions including cardiac disease induced by previous cigarette smoking and other co-morbid conditions. Despite a good selection process that considers clinical status as well as co-morbid conditions, death occurs at a rate of 2.5 % in the authors unit. The causes of death are ventilatory failure, pneumothorax, pneumonia, systemic sepsis, or massive haemoptysis. Careful observation and working closely with an intensive care unit would probably reduce but will not totally obviate death.

- **Failure to respond.** Failure of atelectasis after endo-bronchial valves occurs in 20-40% of cases. Most causes are speculative. This would include a) an under-estimate of fissure integrity, b) opening of collateral channels due to increase pressure c) fault in valve insertion d) migration or displacement of valve (sudden loss of efficacy) and e) opening of accessory bronchi. In all patients where loss of efficacy or failure to respond to valve insertion occur, a combination of CT scan and a bronchoscopy are advised. The reason is to look into wrong placement, peri-valve leak or missing bronchi that needed occlusion.

Evidence of increasing efficacy of EBV insertion:

The effectiveness of the valves has improved with improved selection process. As stated previously, the initial VENT trial found a small improvement in FEV1 and in exercise tolerance in all patients compared with the control arm. The outcome improved in sub-group of patients with highly heterogeneous disease and fissure integrity (Scuirba 2010).

A further sub-analysis of the European patients of the VENT trial found marked improvement in FEV1 and quality of life as assessed by St George's Respiratory Questionnaire when EBV was placed in patients where there is fissure completeness between the target and

the adjacent lobes. Further improvement was found when there were signs of lobe exclusion (collapse) after valve insertion (Herth 2012).

More recently, the results of two prospective clinical trials are presented and are available on abstracts only. The first study was the first double blind sham controlled trial comparing endo-bronchial valve insertion with a sham procedure (Davey 2015). The sham arm consisted of bronchoscopy and Chartis balloon assessment. Of note, the selection criteria were based on fissure integrity only. Although Chartis assessment was made, this did not influence the selection of patients. The primary outcome was change in FEV1.

A total of twenty-five patients of each arm were recruited. At three months, the between group difference for FEV1 was 20.9 % (95% confidence interval of 4.3 – 37.5). There was a decrease of 400 ml for residual volume (RV) and 5.06 points reductions in SGRQ and 33 m increase in the 6 minute walk distance. The rate of volume reduction in this study was approximately 50%.

In another study, sixty-eight patients were randomised 1:1 for endo-bronchial valves and usual care. Patients were randomised only when favourable data from both Chartis and fissure completeness rate on CT scan. The six months results were impressive (Klooster 2015).

Compared to the control group, there was a marked difference in the number of patients achieving minimally important difference in all parameters in the valve treated group compared to the control group. The results included improvement in objective measurements (FEV1 and residual volume) , and in subjective markers (St George's Respiratory Questionnaire (SGRQ) and 6 minute walk distance. No placebo arm was used in this study.

A recent analysis showed that the efficacy of valve insertion as judged by subjective and objective parameters continued after one year although with some reduction in the magnitude for all parameters (Klooster 2016).

At the time of writing this article (November 2016), the results of the largest prospective trial (the LIBERATE trial) has not been published. LIBERATE trial is a prospective randomised control trial with 2:1

(valves: control) randomisation. The trial recruited 187 patients and has been run in over 50 centres in the US, two centres in the UK and one centre in the Netherlands. Patients included were those of high heterogeneous emphysema, over 80% fissure intactness and a CV negative pattern on Chartis tracing.

The study has two-phase follow up: 12 months after which a cross over phase start and 5 years follow-up for long term efficacy including mortality rate. The study is expected to report in the spring of 2018 for phase 1 and 2022 for phase 2.

Endo-bronchial coils:

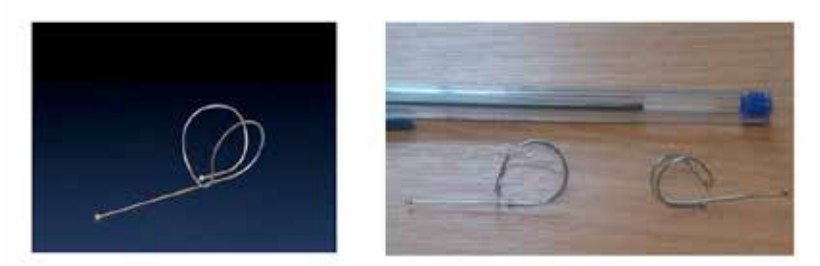


Figure 27: Endo-bronchial coil – Two coils compared to a size of a writing pen.

Coils are nitinol wires with a predetermined shape (figure 27). They are inserted through a leading catheter. The, birth-shape' is formed inside the bronchial tree. An average 10 coils are inserted in each lobe (figure 28) aiming at treating two lobes. The treatment is normally bilateral with 1-4 months separation time between the two procedures. Coils are permanent devices that are not reversible or removable once inserted. It is thought that coils act by 3 mechanisms:

1. Volume reduction by folding lung tissues.
2. Increasing elastic recoil of the emphysematous areas
3. Supporting small and medium size airways that are likely to collapse during expiration.

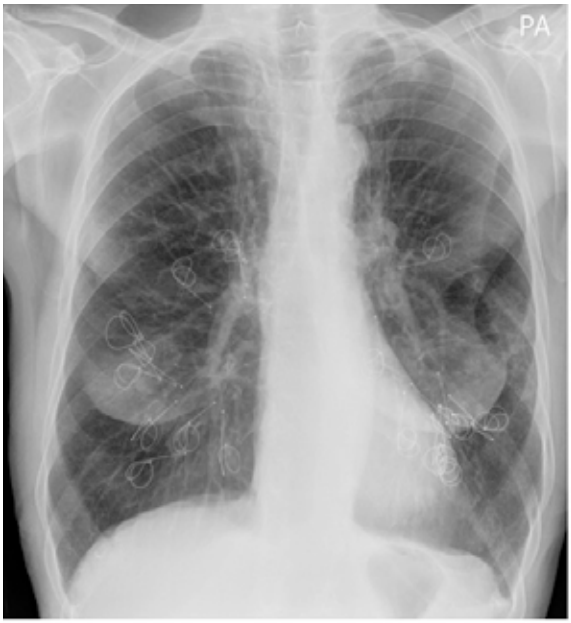


Figure 28: Bilateral coils inserted in the two lower lobes

Coils are inserted under image intensifier (figure 29) under heavy sedation of general anaesthesia. The efficacy of the coil is not affected by absence of collateral ventilation or by the degree of heterogeneity of emphysema.

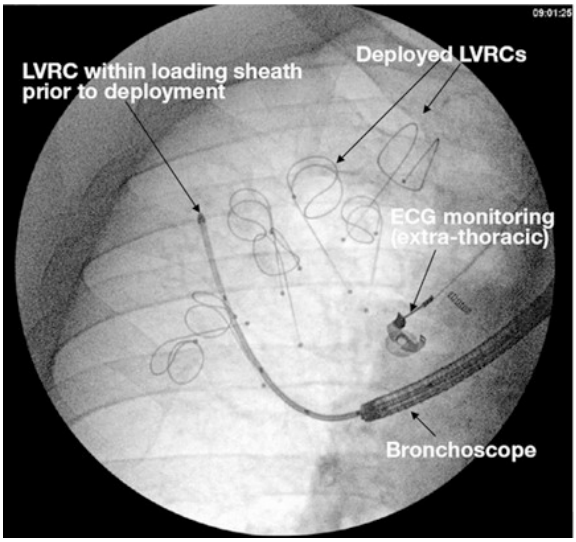


Figure 29: Lung volume reduction coils (LVRC) are inserted under the direction of image intensifier (direct vision fluoroscopy).

Several open feasibility studies found that coil insertion was safe. These were reported by Herth 2010, Selbos 2012, Klooster 2014 and Deslee 2014. In the first randomised prospective trial by Shah (2013) et al (the RESET trial) described benefit of endo-bronchial coils after three months in patients with homogeneous and heterogeneous emphysema. In the 47 patients recruited 23 received coil treatment. The main aim of the study was improvement of SGRQ.

The study found a significant improvement at SGRQ in the coil group after ninety days. The study also reported improvement in other secondary outcome measures. The main adverse events occurred in the first months. This included two pneumothoraces and increase in the rate of exacerbations. Between 30-90 days, no adverse events were described.

The effect of coil in patients going into the RESET trial was re-examined twelve months after coil insertion (Zoumot 2015). Reduced efficacy was seen in all study end points. However, the improvement of benefit remains clinically significant for SGRQ, Residual Volume and for FEV1 and 6-MWD. The study found similar benefit in homogeneous and heterogeneous emphysema.

Similar findings were reported in a pan-European prospective, open label twelve months study (Deslee 2014).

Two large prospective clinical trials using endo bronchial coil were recently described. The first was performed in France - the REVOLENS study (2016) and the second was conducted in the US- the RENEW study.

The REVOLENS study recruited one hundred patients from ten French Hospitals. The aim of the study was to investigate efficacy (by looking at 6-MWD), side effects and economical value of endo-bronchial coils. The study found a significant improvement of 6-MWD, FEV1 and SGRQ in the coil group compared to those with usual care. This improvement was maintained for a year. There was a slight increase in adverse effect in the coil group with regards to pneumothoraces and COPD exacerbations. There were four deaths in the coil group and three in the usual care arm.

Several shortcomings were reported for the REVOLENS study. Significant improvement was due to decline in these parameters in the control group rather than improvement in the coil group. Patients were included without standardisation of the CT scan and finally patients on oxygen therapy (60% of patients) were not allowed oxygen during the 6-MW test.

The RENEW study (Scuirba 2016) is the largest clinical trial on coil to date. The trial recruited 315 patients with randomisation rate of 1:1. The main end-point of the study was the difference in 6 MWD at twelve months between coil insertion and standard care. Half way through the study, inclusion criteria were extended to include patients with less hyper-inflation (RV over 175% of expected values).

The study reported a modest improvement in primary end-point for all patients. Between the group difference was 14.6 m in 6-MWD in favour of the coil with 40 % achieving the 26 m – minimal clinically improvement difference. The improvement of SGRQ was more significant with a mean between-the-group difference of -8.9 points in favour of the coil group.

A subgroup analysis found greater benefit from coil treatment measured by several end points with hyper-inflation (Residual volume of 225% predicted). The discussion of the study however pointed out that a cut-off point of 200% of predicted was a better discriminator for likely responders.

For the first time the study distinguished between post coil pneumonia and post coil reaction to the tension induced by insertion of several coils. The studies demonstrated that those with post coil consolidation tended to respond more favourably and for a long period of time to coil insertion.

Further analysis found that when coils were inserted bilaterally into the lobes most affected with emphysema by QCT scans, the objective and subjective benefits have significantly increased (Shah 2017 – American Thoracic Society Conference – Washington DC).

Sclerosing agents:

Sclerosing agents (hot steam and air seal polymers) have been tested in emphysema. The two methods create lung inflammations in the treatment site that would result in localised fibrosis followed by volume reduction.

Prospective studies investigating safety and efficacy have been done for both agents.

- **Hot water vapour- Steam:**

Figure 30: A schematic presentation of the water vapour deployment system

This procedure uses thermal energy from heated water vapour (figure 30) to induce inflammation followed by lung fibrosis which leads to volume reduction in the treated area (figure 31).

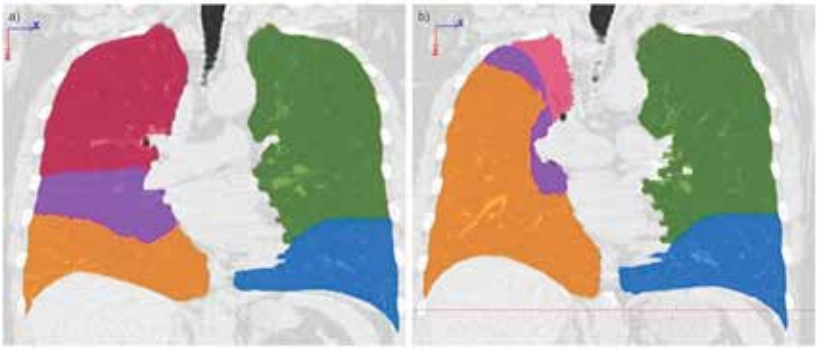


Figure 31: A coronal CT scan of lung lobes before (left) and 6-months after (right) of treatment of the right upper lobe with single episode of water vapour treatment. Note the loss of volume in the right upper lobe and the expansion in volume of the right lower lobe. From Snell et al (2012)

The obvious concern is that this procedure can result in uncontrolled inflammation manifested with pneumonia-like symptoms of fever, breathlessness, haemoptysis, chest pain and fatigue.

The first study to report benefit of the steam therapy was published by Snell et al in 2012. This was an open label study of forty-four patients run in two centres in Australia and Europe. Patients had severe predominantly upper lobe emphysema. At six months there was improvement in most lung function tests and in all components of SGRQ. In addition, there was an impressive volume loss averaged over 700 ml in the treated lobes.

Significant side effects were noted, but all were predictable. These included pneumonic symptoms of cough, fever, chest pain and haemoptysis. Death occurred in only one patient, sixty-seven days from receiving water vapour treatment.

A further trial (STEP-UP) trial was reported in 2016 (Herth 2016). This was a 2:1 randomised trial in patients with highly heterogeneous emphysema and upper lobe predominant disease. Notably, in this trial, hot water vapour was instilled in the target lobe at two stages

three months apart. At the second stage up to two segments were treated. Calculation of tissue-to-air ratio was made on HRCT scan to work out the amount of vapour needed to deliver. The main two end points were change in FEV1 and SGRQ.

A total of 134 patients were included. At six months the study achieved all its end points. FEV1 improved by 14.7%, residual volume decreased by 300 ml and SGRQ score decreased by 9.7 points. Clinically important difference was seen in 50% of all patients receiving steam compared to 13% in the control arm. Increased inflammatory symptoms were seen in the 18% vs 8% in the treatment groups with one death three months after treatment with water steam.

One of the initial shortcomings of the STEP-UP trial was in its design. For a trial where the subjective SGRQ is one of its components, a group receiving sham procedure would strengthen the findings of the study.

A follow-up letter to the Lancet Respiratory Medicine, Shah et al (2016) reported that the benefit of the treatment extended to 12 months following the treatment (figure 32).

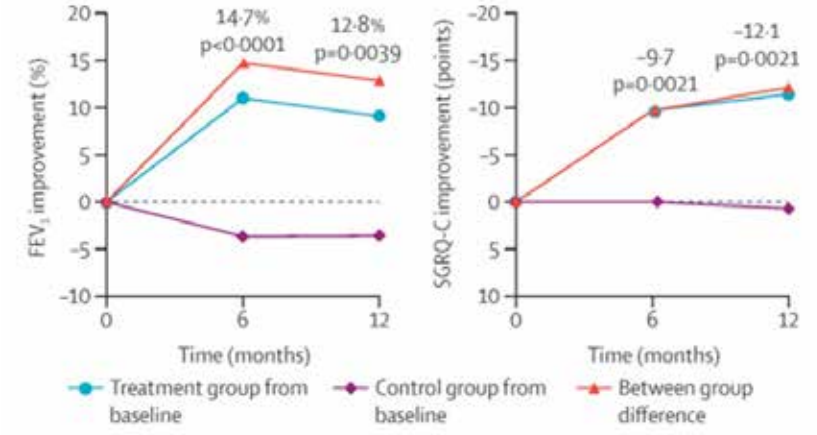


Figure 32: Improvement of FEV1 and SGRQ at 6 months and 12 months after sequential treatment with water vapour. Hearth 2016 (for the 6 months) – and Shah 2016 (for the 12 months results)

More work need to be done in patients with lower lobe disease. The number and intensity of treatment needs to be evaluated. The benefit-risk analysis needs to be further evaluated. However, given the fact that water is the only agent used, this treatment is very promising and may be used on wider scale worldwide.

- **Aeri-Seal foam treatment:**

The Aeri-Seal system introduces a polymer material aims to the small airways and alveoli. The material is thought to function by preventing air entering the alveoli, closing inter-lobar collateral channels and create a film on the surface of the alveoli and the small airways. At a later stage an inflammatory process ensues that result in volume reduction (Figure 33).

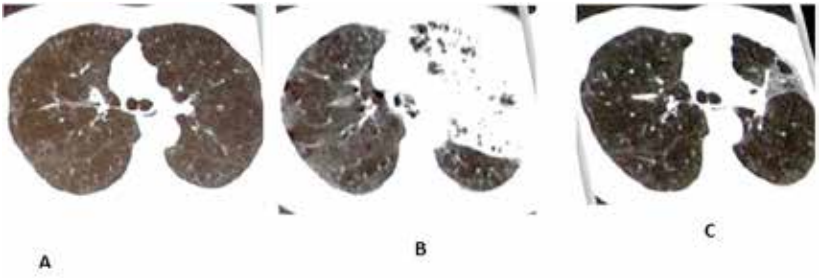


Figure 33: Three CT scans of a patient treated with air sealant in the left upper lobe. A. Before the treatment B. 3-weeks after treatment showing pneumonic changes and C. 3-months after treatment showing volume reduction in the treated lobe with fibrosis.

The material used is a combination of aminated polyvinyl alcohol, glutaraldehyde and air. The mixing process needs to happen quickly and so is the introduction of the foamy material through a catheter to the target area (figures 34). Unlike water vapour, where the inflammatory reaction occurs few days to weeks from the treatment, signs of respiratory symptoms in the Aeri-Seal occur within twenty-four hours.

The ASPIRE study was designed to investigate prospectively the Aeri-Seal in patients with upper lobe emphysema. The trial aimed at

Figure 34: The set used to inject aer-sealant. The two material known as solution a and b. The mixing syringe and the catheter used in deployment of the mixed solution. The injection needs to be done within less than 60 seconds from completion of the mixing process.

recruiting 300 patients. The study had to be terminated after involving only 95 patients due to lack of financial resources. The physicians involved in the study, took it upon themselves to analyse the data available at three and six months.

Most of the analyses were limited due to the small number of patients. Data from the first three months are seen in figure 35.

Data at six months was available on only twenty-one patients. Nevertheless, a clinically significant improvement in FEV1, 6-MWD and SGRQ was seen in 18%, 18% and 72% respectively.

Two deaths occurred in the treatment group and inflammatory adverse effects were seen in 44% of the candidates.

More recently the right of ownership has been bought by PulmonX

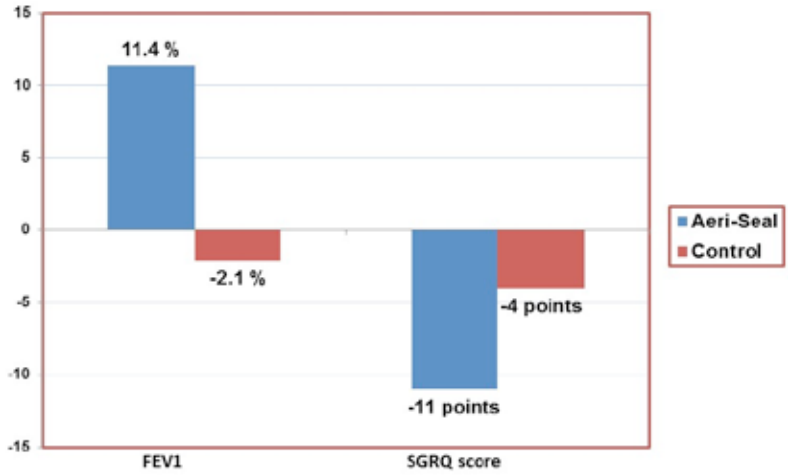


Figure 35: Change in FEV1 and SGRQ after at 3 months after Aeri-Seal insertion.The results persisted at the 6 months point. (Come CE 2016.)

(the owner of the Zephyr endo-bronchial valve) who are undertaking steps for multicentre, placebo control trials on a treatment approach that involve small doses of AeriSeal over several treatment periods in a similar way to the STEP-UP trial for water vapour.

Heterogeneous versus homogeneous emphysema

Unlike the previous thinking, it is rarely that we see total homogeneous emphysema. Modern HRCT scans and particularly quantitative HRCT scans show heterogeneity. Heterogeneity of emphysema is defined as the difference in lung destruction between two adjacent lobes.

The cut-off point which defines homogeneous and heterogeneous emphysema is not clear. The LIBERATE trial defined heterogeneity of 15% difference between the target lobe and the adjacent lobe.

Clinical trials showing useful results for endo-bronchial valves and endo bronchial coils with less heterogeneity present. Valipour et al (2015) reported that in the IMPACT study an improvement in FEV1

and SGRQ in patients with 'homogeneous' emphysema (2015). Kemp et al (American Thoracic Society Meeting May 2017- not published as a manuscript yet) demonstrated further improvement in almost all subjective and objective parameters in the TRANSFORM Study where heterogeneity was less than 15%.

The Stelvio study (Klooster 2015) also compared the efficacy of endobronchial valves in homogeneous and heterogeneous emphysema using the 15% difference as a distinguisher. The study found that valves were useful in both, but more so in heterogeneous emphysema.

For coil insertion, the RENEW Study found no difference according to homogeneity of the disease.

Therefore, the concept of heterogeneity of emphysema has lost its impact on patient's selection. For valve insertion it is the absence of collateral ventilation that is important. For coil insertion, it is the greater residual volume and the insertion of coils in the most destructed lobes that matter.

The optimal outcome of volume reduction therapies:

Various clinical trials of methods of lung volume reduction therapies used different main outcome. Valve trial all used FEV1 as the main outcome. Other objective outcome measures were used. These included reductions in residual volume and the 6-MWD. Subjective measures such as health related quality of life, mainly SGRQ was also used.

Surgical trials including the NETT trial used survival as the main outcome. Non-valve studies used 6-MWD for coils and SGRQ for steam as the principal outcome. Composite outcome including BODE score was used in one analysis as a surrogate marker for survival (Valipour 2014) .

Outcome used in trials published thus far is outlined in figure 36.

It is the author belief that, for future studies, one objective assessment and one subjective assessment should be used for all methods as main outcome.

Study	Year	Device	Primary outcome
VENT	2010	Valve	FEV1
RESET	2013	Coil	QoL (St George's)
Stelvio (2015), IMPACT (2016) and LIBERATE (ongoing)	2018	Valve	FEV1
RENEW	2016	Coil	6' walk distance
Deslee (European Trial)	2014	Coil	QoL St George's
NETT	2003	Surgery	Exercise capacity-Survival
Believer HiFi	2013	Valve	FEV1
Coil European Registry Study	2018	Coil	QoL St George's
STEP-UP Trial	2016	Thermal vapour	FEV1 & St George's

Figure 36: A table showing outcome used in large clinical trials. Note that FEV1 was the main outcome in all valve studies but in none of the studies investigated using other methods of treatment.

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