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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.

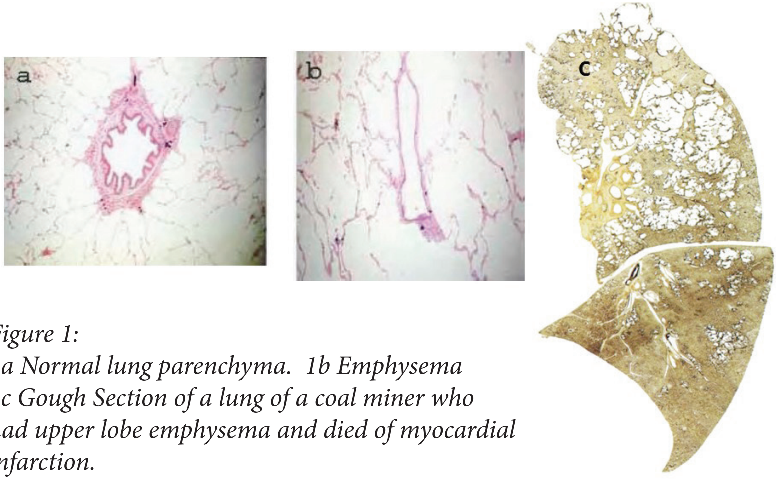



*Figure 1:*
*1a Normal lung parenchyma. 1b Emphysema*
*1c Gough Section of a lung of a coal miner who had upper lobe emphysema and died of myocardial infarction.*

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).

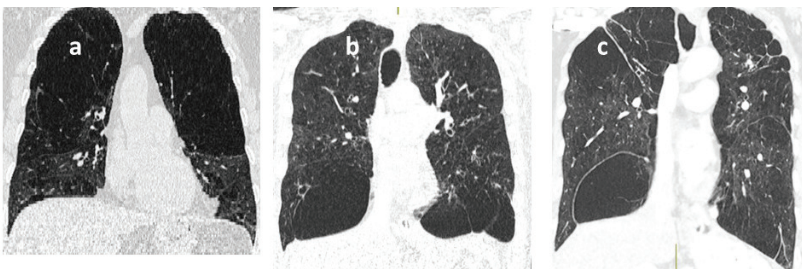



*Figure 2: Coronal CT scan in 3 patients. –*
*Upper lobe emphysema (a),*
*lower lobe emphysema (b)*
*and patchy emphysema with bullous formation in the right lower lobe ( c ).*

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).

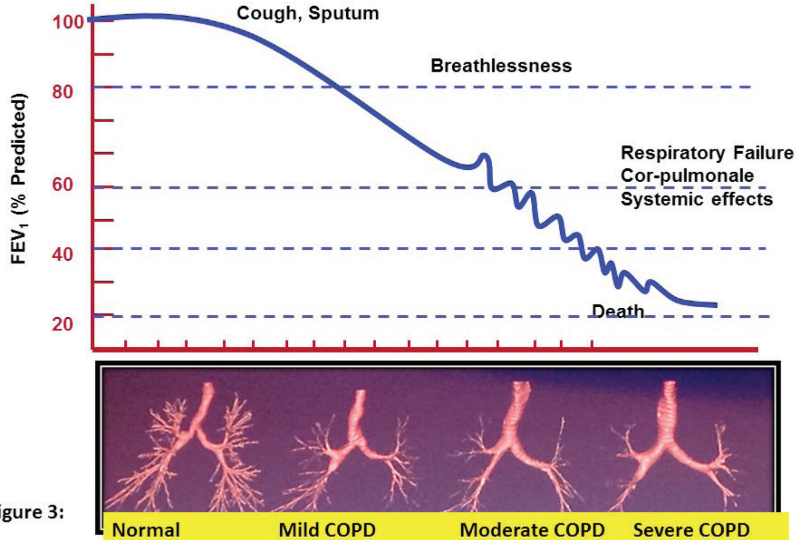



Figure 3:

*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).

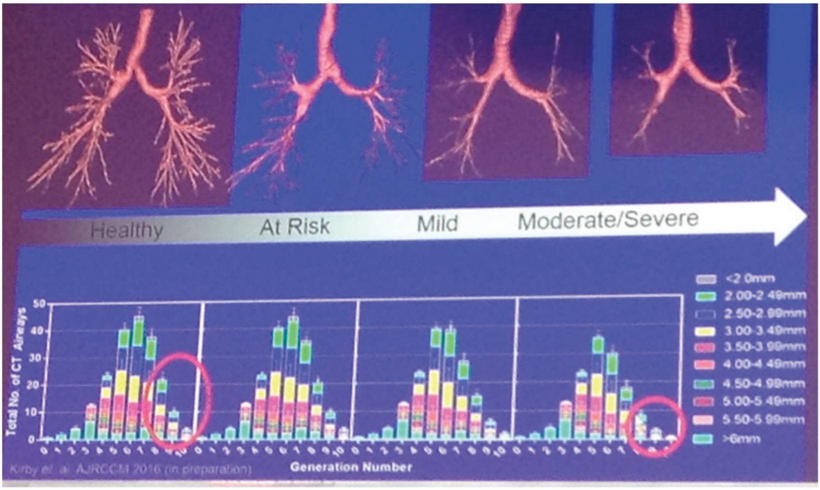



*Figure 4: The bronchial casts of patients with emphysema – below this is a histogram showing the gradual loss of small airways on quantitative CT scans (red circles) Slide from Hogg J – ERS 2016*

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).

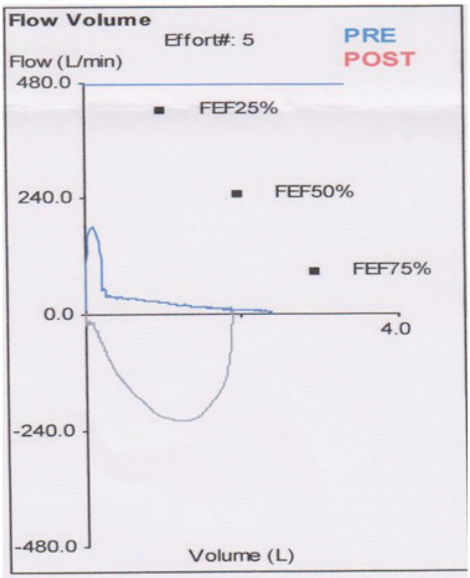



*Figure 5:*
*Typical flow-volume loop for emphysema. Note the sudden reduction of flow accounted for by collapse of moderate size and small airways at forced expiration.*

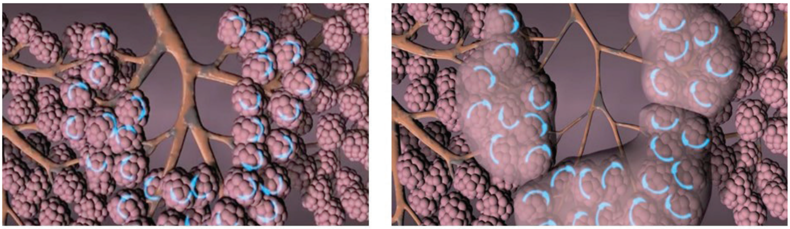


*Figure 6: A schematic representation of (a) normal airways with intact number of small functioning airways and alveoli as well as good size airways and (b) emphysematous lung in which there is fusion of the alveoli causing air-trapping represented by the blue arrows and thinning of the airways. The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

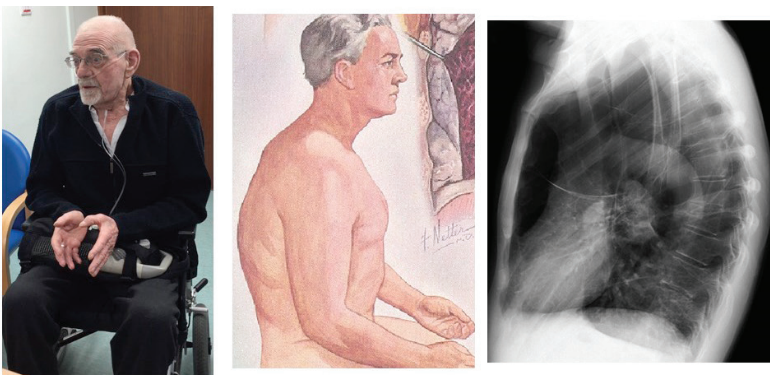


*Figure 7: A patient with emphysema (a) – please note the reduced body mass index and the pursed lip breathing. (b) a schematic representation of the increase in anterior-posterior diameter (kyphosis) and ( c ) a lateral chest x ray of the patient confirming the kyphosis induced by lung hyper-inflation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

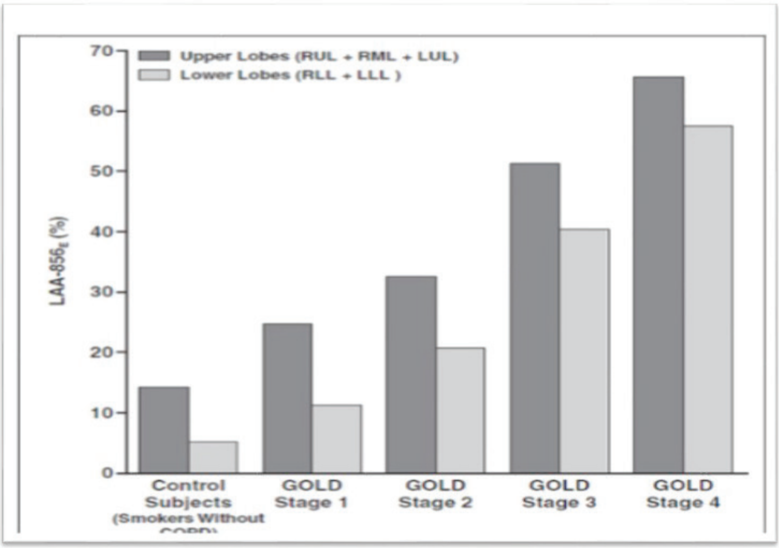



*Figure 8a: Prevalence of emphysema expressed as Low Attenuation Area (LAA) on HRCT scans of patients with different GOLD stages depicting declining values of FEV1. Please note that when FEV1 declines below 60 % of predicted there more than 40% likelihood of patient having emphysema. From Schroeder 2013*

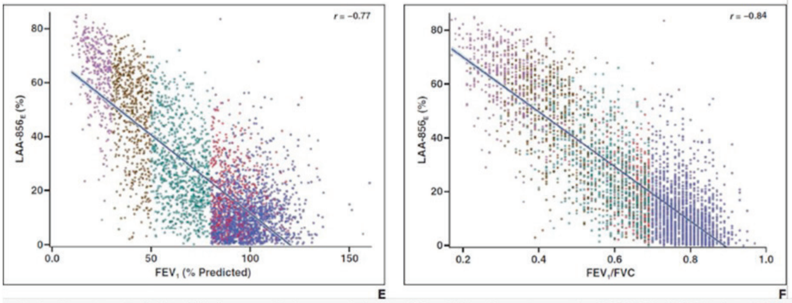



*Figure 8b: The proportion of emphysema space on HRCT scan expressed as the Low Attenuation Area (LAA) Versus FEV1 (left) and the degree of Airflow obstruction expressed as FEV1/FVC ratio (right). This and figure 8a showed that not only the presence of emphysema but the extent of emphysema increases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

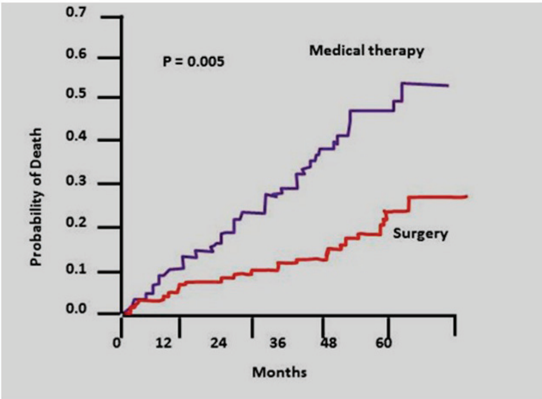



*Figure 9: Favourable survival curve in surgically treated patients in a sub-group of patients in the NETT trial – those with upper lobe emphysema and poor exercise tolerance.*

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).

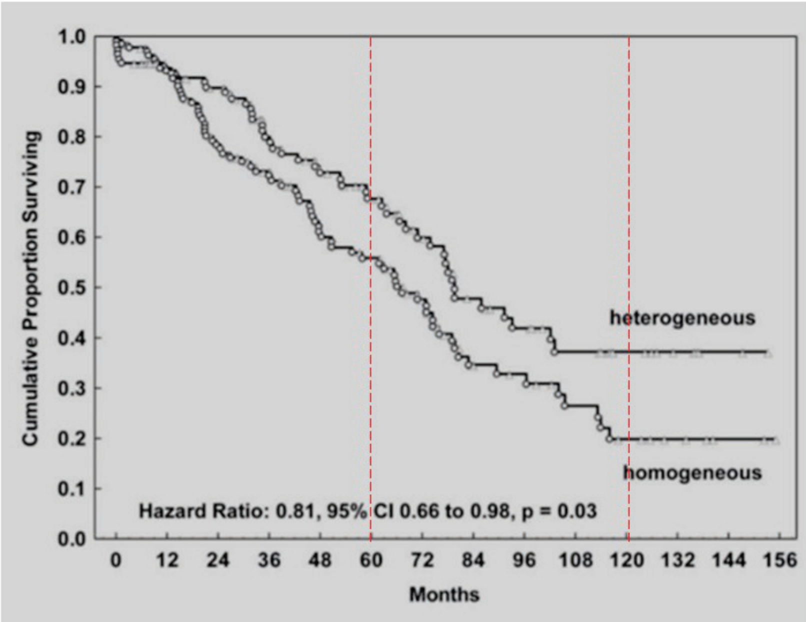



*Figure 10: Favourable survival curve without transplant in surgically treated patients with heterogeneous and homogeneous emphysema. Weder (2009). Note the high survival rate at 5 and 10 years, in particular for patients with heterogeneous emphysema*

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<br>Undergone pulmonary rehabilitation programme |
| Modified MRC Breathlessness Score >2<br>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'<br>(degree depends on the proposed procedure valves, coils or surgery) |
| No major co-morbid conditions |

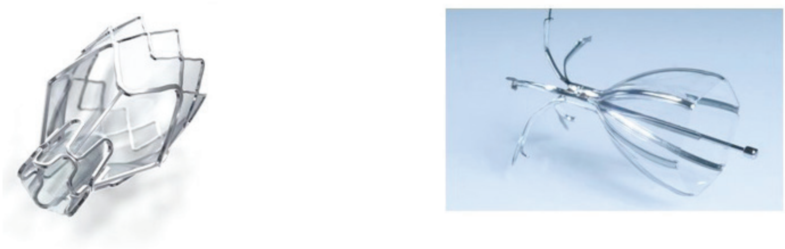
*Table 1 b*

*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).



A B

*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).

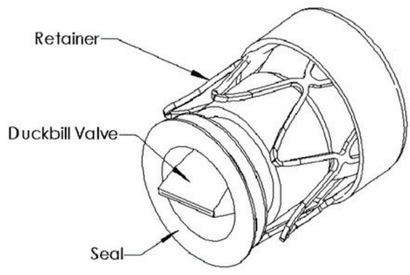



*Figure 12: The emphasis valve (the first generation of zephyr valve). The valve consists of a retainer made of a nitinol cage, a seal made of silicon and the valve itself (duckbell) valve made of Silicon. The first animal and clinical work was published by Dr Gregory Snell (right) – (Snell 2003).*

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.

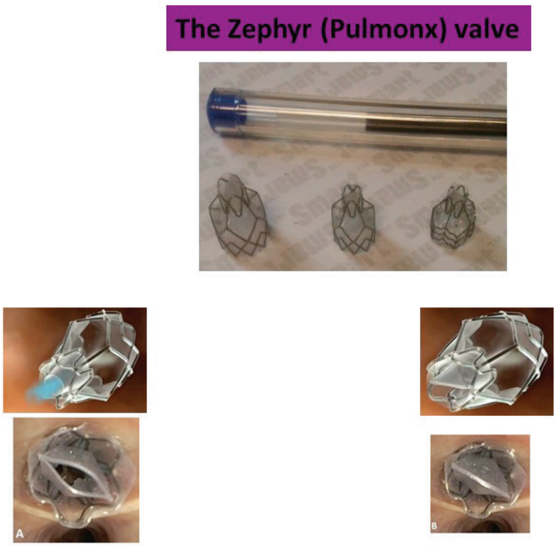



*Figure 13: The 3 sizes of the Zypher valve (above). The valves are the size of peanuts. The sizes are made to fit several size bronchi. Below an animation of the valve opening during expiration (A) to allow air and secretion to leave the lobe and closes during inspiration (B).*

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.

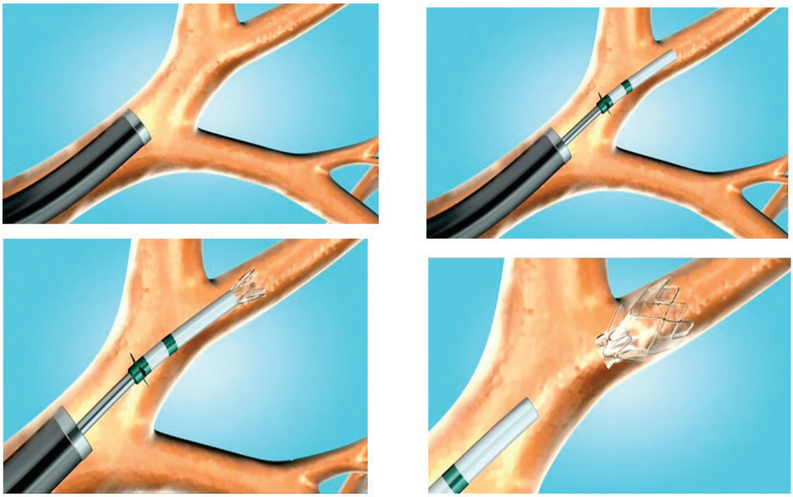


*Figure 14: Image capture of insertion of an endo-bronchial valve in the apical segment of the left upper lobe.*

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.

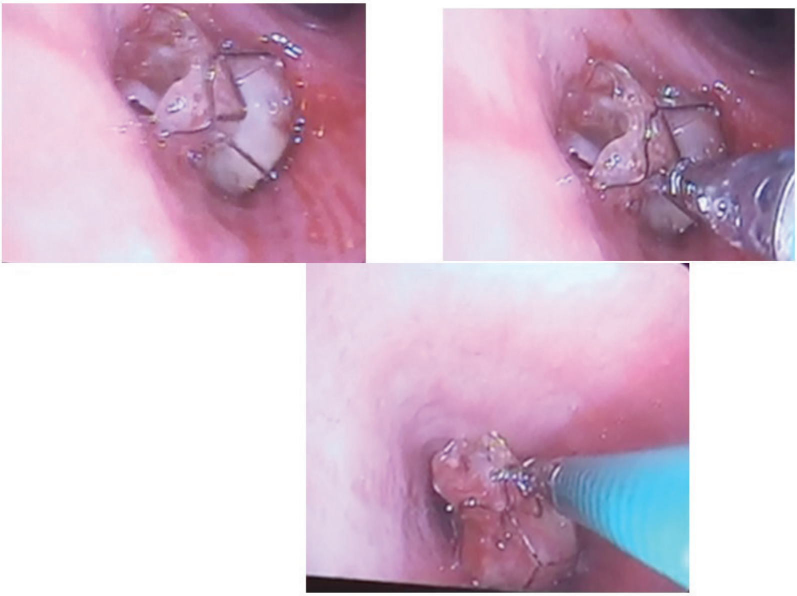


*Figure 15: Removal of a misplaces endo-bronchial valve.*

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

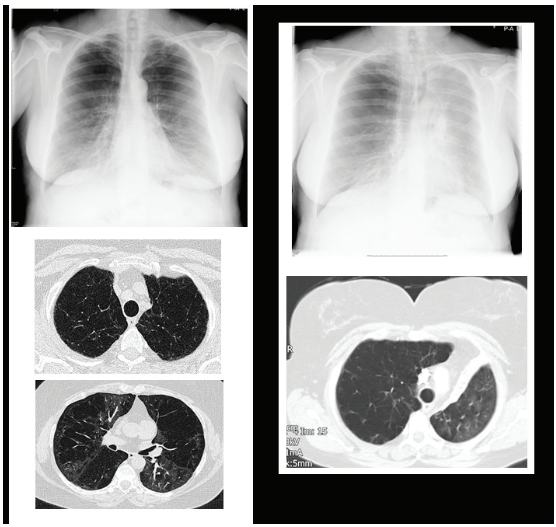
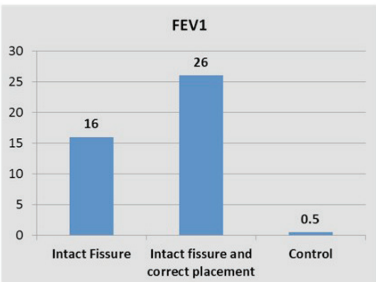


*Figure 16:*

*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).



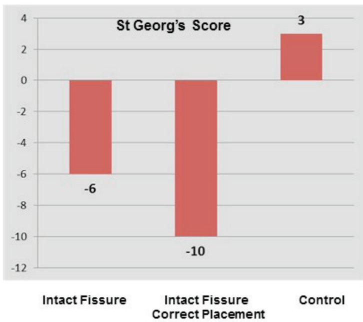




*Figure 17: The results of the European Cohort of the VENT study. Please note a significant and meaningful improvement in FEV1 and SGRQ after insertion valves when the inter-lobar fissure is intact and after correct insertion resulting in lobe atelectasis. (Herth 2012)*

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).

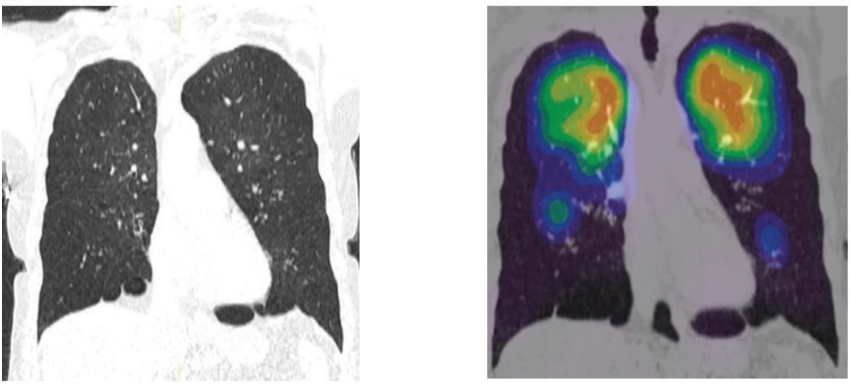


*Figure 18: A single photon emission computed tomography (SPECT) in a 61 year old patient with lower lobe emphysema and heterozygote alpha1 anti-trypsin deficiency. Note that the CT scan (left) under-estimates the differential uptake illustrated on the SPECT scan.*

*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).

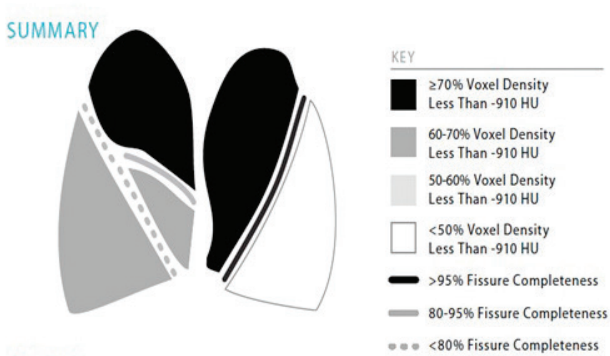
Patients with intact fissures who were treated in the VENT study (Scuirba 2010) in both arms achieved good improvement in FEV1, SGRQ and 6 MWD. A retrospective analysis has shown, that in this group, a continuous improvement in FEV1 and significantly high survival after five years of valve insertion.

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).




RESULTS

| | RIGHT LUNG | | | | LEFT LUNG | |
|---|---|---|---|---|---|---|
| | RUL | RUL+RML | RML | RLL | LUL | LLL |
| % Fissure Completeness | 64.2 | 65.0 | 84.9 | 65.0 | 100 | 100 |
| % Voxel Density Less Than -910 HU | 84 | 79 | 63 | 66 | 83 | 43 |
| % Voxel Density Less Than -950 HU | 67 | 59 | 36 | 40 | 69 | 16 |
| Inspiratory Volume(ml) | 1120 | 1492 | 372 | 1901 | 1717 | 1520 |

*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):*

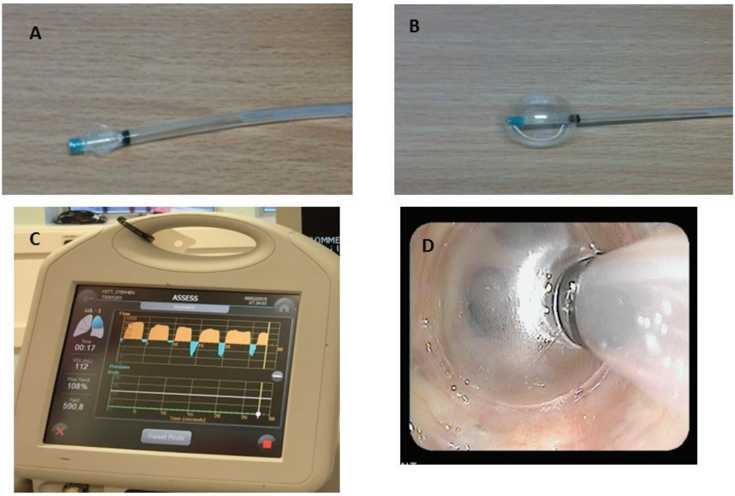
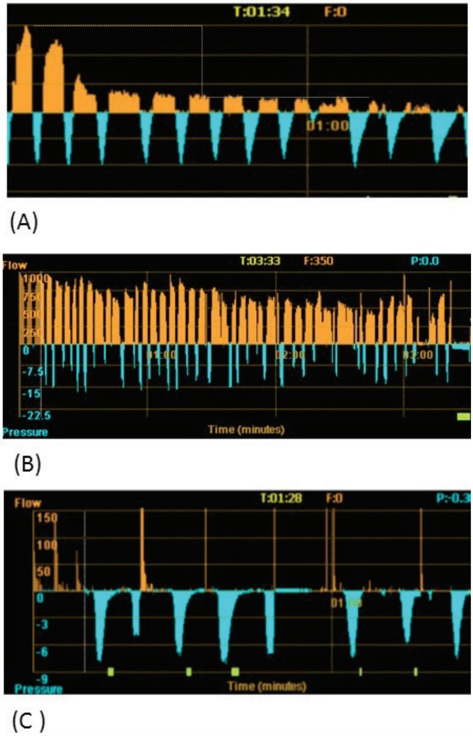



*Figure 20: The Chartis catheter deflated (A) and inflated (B), the Chartis console [c] and the Balloon catheter inflated in the left upper lobe.*

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.