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Landmark papers in respiratory medicine

The STELVIO trial, a game changer for bronchoscopic lung volume reduction in patients with severe emphysema

Chronic obstructive pulmonary disease (COPD) is characterised by persistent respiratory symptoms and airflow limitation, which is caused by small airway disease (bronchiolitis) and alveolar destruction (emphysema) [1]. Patients primarily suffering from severe emphysema are often limited in exercise capacity due to the consequences of hyperinflation [2].

Reducing hyperinflation has already been proven effective in lung volume reduction surgery (LVRS), in which selected areas of hyperinflated lungs are resected [3]. The National Emphysema Treatment Trial, in which patients with severe emphysema were randomised to either undergo either bilateral LVRS or optimal medical treatment alone, demonstrated an improvement in forced expiratory volume in 1 s (FEV_1) and exercise capacity in the intervention group. Lung volume reduction improves ventilatory mechanics through various mechanisms:

- improving lung elastic recoil
- reducing dead space
- relieving alveolar compression on relative preserved lung parenchyma
- improving respiratory muscle kinetics

While LVRS is effective, its invasive nature and potential complications make it underutilised, with low implementation in clinical practice. Bronchoscopic lung volume reduction (BLVR) arose as a potential minimally invasive intervention in which hyperinflation was targeted endoscopically by using various devices, such as endobronchial valves (EBVs), coils, sealant and thermal vapour [4–6].

EBVs are one-way valves placed in the bronchi *via* a bronchoscope aiming to seal an entire lobe where only air can escape without allowing new air to enter, which induces atelectasis and causes lung volume reduction [7].

BLVR using EBVs is now an evidence-based intervention for patients with advanced emphysema, incorporated into international guidelines such as those of the Global Initiative for Chronic Obstructive Lung Disease [1] and National Institute for Health and Clinical Care Excellence [8]. BLVR has come a long way since the first trials started decades ago. Indeed, it was an extensive learning journey in which adequate patient selection turned out to be a key factor in achieving clinically meaningful results (figure 1). The STELVIO trial was a real game changer for EBV therapy as for the first time, clear positive results were demonstrated by selecting the right patients to treat, based on a detailed *post hoc* responder analysis of the previous trials [9].

Indeed, the Endobronchial Valve for Emphysema Palliation Trial (VENT) [9] in 2010 was the first prospective randomised controlled trial using one-way valves unilaterally in patients with severe emphysema. It showed improvements in FEV_1 and 6-min walking distance (6MWD), but the effects were modest and did not meet the threshold of the minimal clinically important difference. Importantly, VENT also identified variables that were

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The STELVIO trial was crucial to ensure that bronchoscopic lung volume reduction using one-way valves has evolved from an experimental intervention into a state-of-the-art treatment option for specific patients with advanced emphysema http://bit.ly/2IgMrsp

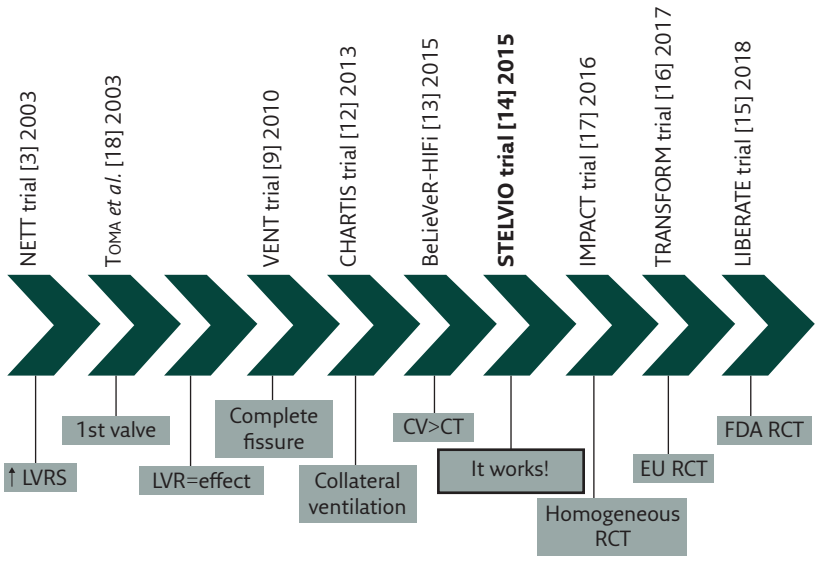

Figure 1 *Timeline of important studies in the field of interventional lung volume reduction (LVR). RCT: randomised controlled trial; EU: European Union; FDA: Food and Drug Administration.*

possible predictors for response, like emphysema heterogeneity and fissure integrity. Fissure completeness and complete lobar occlusion were predictors of treatment success.

Fissure completeness is thought to be a surrogate marker for interlobar collateral ventilation (CV). If CV is present, air can enter the targeted lobe by its collaterals, in which case, atelectasis does not occur. The subgroup of patients in VENT with complete fissures demonstrated improvements in FEV_1 of 16.2% at 6 months, while no difference was observed on the 6MWD.

Assessing fissure completeness and the size of fissure defect on high-resolution computed tomography (HRCT) is challenging, with known interobserver variability [10]. In addition, there is no clear cut-off value of percentage of fissure integrity that precisely predicts the absence of CV [11]. Hence, a direct measurement of CV before placing EBVs was needed to select patients who are most likely to achieve atelectasis and have clinical benefit.

The Chartis system (PulmonX, Redwood City, CA, USA) allows measurement of CV [12]. It entails the insertion of a catheter trough the working channel of a bronchoscope. The catheter has a balloon at the end that when inflated, seals off the target lobe. At the tip of the catheter, a central lumen allows air only to flow out. Measurement of this flow permits assessment of CV: if the flow slowly decreases to zero, there is no indication of interlobar CV and EBVs can be placed. The BeLieVeR-HIFi study showed that the Chartis measurement could reliably identify the absence of CV and predicted treatment success [13]. The four patients in this study who had visual intact fissures on computed tomography but were CV-positive with Chartis measurements showed no benefit after valve placement.

The STELVIO trial, a single-centre randomised controlled trial, published in December 2015 in the *New England Journal of Medicine*, combined the knowledge gained from VENT with the reliable new way of measuring collateral ventilation to accurately select patients with severe emphysema and static hyperinflation to treat with one-way EBVs compared to standard medical care [14]. The exclusion of candidates who were CV-positive was unique in this trial design.

Patients with severe emphysema who had stopped smoking for ≥6 months were considered study candidates if they had post-bronchodilator FEV_1 <60% of the predicted value, increased total lung capacity and a residual volume >150% of the predicted value. Aside from lung function criteria, patients had to be highly symptomatic, with a dyspnoea score on the modified Medical Research Council scale >1. Furthermore, specific radiological characteristics were required: visual severe emphysema on HRCT with a complete or nearly complete fissure between the target lobe and an adjacent lobe. Quantification of emphysema to classify the distribution as homogenous or heterogenous was performed after study completion using computerised quantification software on the baseline HRCT. Patients who met inclusion criteria underwent randomisation 1:1 between the EBV intervention arm and the control group. Baseline characteristics of the two groups were similar except for a difference for female sex, which was more prevalent in the control group.

84 patients were screened, of whom 13 were excluded due to CV and three because of unsuitable airways for EBV placement. A total of 68 patients underwent randomisation, of whom 34 received EBV placement.

The study demonstrated, in the intention-to-treat population, a between-group difference of +140 mL in FEV_1 and +74 m in 6MWD in favour of the EBV group. These outcomes are fairly impressive in this highly symptomatic patient population for which few treatments options exist.

Serious adverse advents were significantly higher in the EBV group (23%) as compared to the control group (5%), of which pneumothorax and exacerbation leading to hospitalisation were the most frequent.

The STELVIO showed that EBV treatment in patients with severe emphysema and proven absence of CV offers an improvement in lung function, exercise capacity and quality of life (as measured by the St George's Respiratory Questionnaire and Clinical COPD Questionnaire). The elimination of patients with CV in this trial led to better outcomes than earlier studies and was the landmark study that lit the way to designing multicentre studies confirming the results and clinical implementation [15–18].

The success of STELVIO undoubtedly led to an incentive for research for interventional pulmonology, specifically BLVR, as well as developments in imaging of emphysema and renewed interest in LVRS. STELVIO helped to ensure that BLVR using one-way valves has evolved from an experimental

intervention into a state-of-the-art treatment option included in international leading guidelines. BLVR with EBV is currently being implemented worldwide. Monitoring implementation in real-life practice and efficacy of long-term results are now key aspects of this therapy.

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Conflict of interest

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