Bronchoscopic Lung Volume Reduction Is Springing with Potential for Patients with Homogenous Emphysema

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COPD is currently the third leading cause of death globally [1] and has a prevalence of >5% in both Europe [2] and the USA [3]. It is the cause of physical impairment, incapacity and a reduced quality of life as well as extensive utilisation of healthcare resources. Reducing the volume of hyperinflated lungs is a logical approach to treatment, especially if this can be achieved by removing or shrinking the most diseased portions of the lung, thereby contributing to the least gas exchange. Lung volume reduction surgery, where the worst affected areas of emphysematous lungs are resected, improves survival and quality of life, but is associated with significant morbidity and a 5.5% mortality [4]. The message from the NETT (National Emphysema Treatment Trial) and a Cochrane collaboration analysis was that patients with homogenous emphysema have the greatest risk for mortality and morbidity [4, 5]. Thus, a view developed that only a minority of patients with emphysema, those with heterogeneous upper-lobe disease and a low exercise capacity benefitted, and then at a high financial cost. There has therefore been a push in the last decade to develop simpler, safer and cheaper methods of emulating the volume loss achieved by surgical resection.

Unidirectional endobronchial valves were the first to be used in human trials and appeared promising [6].

However, perceptions from the NETT study influenced the design of subsequent randomised controlled trials with endobronchial valves [7, 8]. The inclusion and exclusion criteria were similar and the focus was on patients with heterogeneous emphysema. Furthermore, the same CT scoring method was employed. This system is based on visually estimating severity of emphysema in three zones (upper, middle and lower) and scoring them as: 0 (no destruction), 1 (1–25%), 2 (26–50%), 3 (51–75%) and 4 (76–100%). Heterogeneous emphysema was defined as a difference in scores of at least 2 among the three zones in one lung whereas a difference of zero or 1 was classified as homogeneous emphysema. The flaw with this method is that obvious heterogeneous emphysema with 75% destruction in the upper lobe and 26% destruction in the lower lobe is scored as 3 and 2, respectively, and is hence classified as homogeneous disease. Conversely, 76% destruction in the upper lobe and 50% destruction in the lower lobe are scored as 4 and 2, respectively, and with the difference in scores being 2, this is classified as heterogeneous disease. Consequently, some patients may have been included who did not have the optimal emphysema phenotype. Interpreting the phenotypical composition of patients in these studies is also impossible. The consequence is that, although these trials met their end points

with statistically significant results, they did not demonstrate a clinically meaningful benefit. Refinement of treatment strategies with endobronchial valves has limited the population of patients suitable for treatment to those with heterogeneous emphysema and with either an intact fissure or the confirmed absence of collateral ventilation [9].

Weder et al. [10] attempted to visually classify disease according to zonal preponderance as heterogeneous, intermediate and homogeneous. They assessed 250 consecutive patients: 112 with heterogeneous disease, 82 with intermediate disease and 56 with homogeneous disease. For the analysis, they grouped the patients with an intermediate and homogeneous distribution together and demonstrated similar improvements in FEV₁, 6-min walk test and dyspnoea scores. They also reported a persistence of benefit of up to 5 years even though the numbers of patients who contributed to the data dropped off significantly after 12 months. Despite the limitations of this study, there appears to be some benefit for patients with homogeneous or non-heterogeneous emphysema.

The first bronchoscopic therapy to specifically focus on patients with homogeneous emphysema was the airway bypass procedure. The procedure involves creating alternative air passages between the lung parenchyma and segmental bronchi. These new passages are supported by stents and provide an alternative route for gas to escape, circumventing the trapping of gas due to expiratory airway collapse. In principle, this technique is more beneficial for patients with more extensive homogeneous destruction of the lung parenchyma. The initial trial with 35 patients reported improvements in FEV₁ of 7.3% and an increase in the 6-min walk test of 37 m [11]. The randomised, double-blind study recruited 315 patients with homogeneous emphysema. Although there were dramatic improvements within 24 h of the procedure, the effect diminished after 3 months and there was no significant difference between the treatment and control groups at 6 months [12]. The loss of effect was due to stent occlusion, but this effect was diluted due to some patients being inappropriately selected. The trial attempted to safeguard correct selection of patients by using a central radiology laboratory but employed the same flawed methodology as the NETT for defining homogeneous disease.

The tissue sealant 'AeriSeal' was used in an open-label treatment study which recruited 30 patients with homogeneous emphysema and 26 patients with heterogeneous emphysema [13]. There was an improvement of 9.5% in the FEV₁, 16.5 m in the 6-min walk test and in the St. George Respiratory Questionnaire score (−13 points) in patients with homogeneous emphysema. The degree of

benefit in patients with heterogeneous disease was more impressive, with a gain in FEV₁ of 18%, but the high incidence of a systemic inflammatory response following treatment has limited the development of this therapeutic strategy.

A recent randomised, controlled trial of bilateral implantation of lung volume reduction coils (LVRCs) in 46 patients recruited both homogeneous and heterogeneous disease [14]. The pattern of emphysema was determined using quantitative computerised analysis. This study demonstrated a significant between-group difference in improvement in the quality of life as well as in lung function and exercise capacity in the patients when compared to the controls 3 months after treatment [14].

In this issue of *Respiration*, Klooster et al. [15] report on a small prospective study which exclusively treated 10 patients with homogeneous emphysema. The patients were carefully selected on the basis of semi-quantitative analysis of CT scans of the thorax. The study confirmed that treatment with LVRCs leads to clinically and statistically significant benefits which are sustained for up to 6 months after treatment in homogeneous emphysema. Interestingly, unlike lung volume reduction surgery and other bronchoscopic lung volume reduction techniques, treatment with LVRCs does not result in a reduction in lung volume, but there is a reduction in gas trapping. This is consistent with improvements reported for the vital capacity. A number of mechanisms alter compliance in emphysema: a reduction in pulmonary capillary alveolar units which reduces the splinting effect of the pulmonary vasculature, a reduction in the tetherings which maintains patency of the bronchioles and an increase in alveolar volume and surface area which induces changes in the surface tension of the fluid of the alveolar lining. The viscoelastic tissue resistance or frictional resistance from the deformation of thoracic tissues and the frictional resistance to gas flow are factors that affect impedance and may be altered by the insertion of LVRCs. It is plausible that the LVRCs restore the splinting effect in the lung tissue and change the balance in elastic resistance between the lung tissue and the chest wall. The remarkable results observed in the study by Klooster et al. [15] suggest that the balancing forces can be altered by merely treating one lobe. This was despite the presence of widespread homogeneous alveolar destruction observed in this group of patients. This report by Klooster et al. [15] is very welcome as it brings this group of patients with homogeneous emphysema back to the attention of respiratory physicians and it will hopefully stimulate further research and development.

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