Bronchoscopic treatments for emphysema

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Summary  In late stage chronic obstructive pulmonary disease, emphysema can worsen respiratory symptoms, not only via the loss of surface for gas exchange, but also via alterations in mechanical properties of the respiratory system (dynamic and static hyperinflation). Emphysematous lung volume reduction aims at improving respiratory mechanics and symptomatology in patients with advanced emphysema. Lung volume reduction surgery (LVRS) has been shown to be effective in selected patient populations, but its morbidity and costs are quite elevated. Alternatives to LVRS do not remove emphysematous lung tissue per se, but rather consist of devices aiming to: 1) reduce the volume that affected lung parenchyma occupies (unidirectional endobronchial valves or plugs, parenchymal injection of bioactive scarring agents); 2) redistribute ventilatory flow (airway bypass systems). Preliminary studies of these devices have shown that they are relatively safe. These also show modest benefits in exercise capacity, although individual subjects can experience spectacular improvement. Current objective is to identify predictors of response to therapy with such devices.

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Emphysema is characterized by progressive and irreversible destruction of lung parenchyma [1]. It causes incapacitating dyspnoea due to both destruction of the alveoli that reduces the surface area available for gas exchange, and lung hyperinflation that results in changes in respiratory mechanics. These changes in pulmonary mechanical forces and their effect on the inflammatory cascade probably play an important role in disease progression [2]. In the past few years, research has shown that both dynamic and static lung hyperinflation play an important role in dyspnoea in patients with emphysema [2,3].
The medical treatment of emphysema with bronchodilators and inhaled corticosteroids provides some relief, but the majority of patients remain symptomatic despite optimal medical treatment. In addition, smoking cessation, long-term oxygen therapy in patients with hypoxemia and lung volume reduction surgery (LVRS) in a selected population have all demonstrated improvement in survival [3,4]. LVRS can be effective, but sometimes involves excessively high costs and morbidity. Research in the last decade has, thus, focused on alternative, innovative and less invasive methods.

This article discusses various techniques recently developed, and those under development, as well as their physiological basis. To date, most of these techniques are experimental and only a few have been the subject of randomized trials. However, sufficient data can be collected from abstracts, articles and scientific presentations to summarize current and future possibilities for non-surgical instrumental (bronchoscopic) treatment of emphysema.

**Lung volume reduction surgery**

LVRS involves resection of emphysematous lung tissue, usually the upper lobe, with the aim of improving respiratory mechanics by reducing lung hyperinflation and better resizing the lung relative to the chest wall [5,6]. Several approaches have been described for this technique, but it is most often performed bilaterally by thorascopy or median sternotomy, using a linear stapler [5,7]. The National emphysema treatment trial (NETT) study demonstrated a survival advantage with LVRS after a pulmonary rehabilitation program in a subgroup of patients with predominantly upper-lobe emphysema and low-exercise capacity [4].

The principle of "lung resizing" to explain the potential physiological benefit of lung volume reduction in emphysema was first proposed by Brantigan in 1956 and then clarified by Fessler and Permutt in 1998 [8–10]. Thus, resection of diseased lung tissue works by reducing the residual volume and improving the RV/TLC ratio, making the distended chest cavity more compliant and resulting in global improvement in respiratory mechanics. This shows as an improvement in spirometry (FEV1 and FVC), lung volumes and exercise capacity in selected patients; results that were confirmed by the NETT randomised trial [4,9,10].

However, the initial enthusiasm for LVRS faded in the early 2000s, following the publication of several case series and randomized trials showing significant mortality and peri-operative complication rates; mortality ranged from 3 to 19% depending on the cohort and was 5.5% in NETT study patients [4,11–14]. Prolonged bronchopleural air leakage remains the main complication after LVRS [12,14]. The poor cost–benefit ratio associated with this procedure and the potential complications have, thus, led many experts to reconsider indications for LVRS in the treatment of severe emphysema [15–17].

An interest in alternative techniques for lung volume reduction has developed in this context with the aim of making these techniques available to a larger number of patients. Such techniques could, for example, enable provision of lung volume reduction treatment to patients presenting comorbidities contra-indicating surgery.

Furthermore, there is a potential for treatment of predominantly lower lobe emphysema, in which it is believed that pleural adhesions to the diaphragm after LVRS impair diaphragm movement and cancel the benefits of surgery [18,19]. These techniques could also be useful in ventilator-dependent patients to help with weaning; this had been attempted without success with LVRS in patients with respiratory failure requiring mechanical ventilation [20].

- Resection surgery has a poor risk-benefit ratio.
- Instrumental techniques have been explored as alternatives to LVRS.

**Current endoscopic lung volume reduction techniques**

To date, three endoscopic lung volume reduction techniques, all experimental, have been the subject of clinical studies. Most of the data are available as abstracts and presentations with a few case series and a clinical trial in the process of publication. These three techniques use two distinct concepts to achieve a reduction in lung volumes: closure of anatomical airways, and opening of extra-anatomical airways.

**Closure of anatomical airways**

The principle is to block passage of air into a lobe or segment affected by emphysema to obtain its collapse and a reduction in lung volumes [21,22]. This observation is based on atelectasis developing in the lung segments when air passage to them is blocked. This result can be achieved using a device to block lobar or segmental bronchi, or by inducing iatrogenic atelectasis with instillation of a biological adhesive causing lobar collapse [22]. Collateral ventilation pathways between the lobes remain an obstacle to obtaining effective volume reduction, particularly with mechanical airway blocking devices. This is particularly important in emphysema where airways resistance can exceed collateral resistance [23–25]. Devices available to achieve volume reduction include: endobronchial blockers developed by Watanabe, one-way endobronchial valves, and fibrin-based "alveolar glues" [22,26].

**The creation of extra-anatomical airways**

Creating extra-anatomical airways with a special device in a lobe affected by emphysema should make possible the bypassing of the airways that hinder lung emptying. This concept is based on earlier work that studied the possibility of creating shunt pathways between central airways and the zones seriously affected by emphysema [22,27]. A bronchial fenestration system, developed by Broncus Incorporated (Mountain View, CA, USA), is currently under study [28].
Devices currently under study in the endoscopic treatment of emphysema

Endobronchial valves

Endobronchial valves are one-way blocking devices that stop entry of air into the target zone during inspiration while allowing it to escape during expiration. The aim is to induce local collapse due to atelectasis of the obstructed lobe while allowing for drainage of bronchial secretions from the region to reduce the potential risk of post-obstruction pneumonia. Two companies have developed and studied endobronchial valves for the treatment of emphysema: Emphasys Medical (Redwood City, CA, USA) and Spiration Incorporated (Redmond, WA, USA) [7,22].

The Zephyr® valve designed by Emphasys Medical is composed of an outer self-expanding cylindrical metal frame (nitinol: a shape memory alloy) with inside the lumen, a one-way duckbill shaped silicone valve (Fig. 1). This system has been the most extensively studied and has been the subject of a randomized trial whose results will be published soon [29–36]. Zephyr® valves are loaded on a catheter through the instrument channel (2.2 mm) of a flexible bronchoscope. They are then deployed in the segmental bronchi of the lobe(s) targeted for blockage (Fig. 2). For reasons of convenience, precision of insertion and duration, the procedure is usually performed under general anesthesia, but can be performed with success under sedation and local anesthesia [22]. If necessary, these valves can be removed at any time by grasping the metal part with simple biopsy forceps.

Another valve system, developed by Spiration Incorporated, is currently being studied. It has an umbrella design made of silicone covering a nitinol frame. Air can escape around the umbrella but cannot penetrate the target zone during inspiration. The insertion process is similar to that for the Emphasys valve [22,37,38]. This system is currently the subject of a multicenter study and data are available in the form of abstracts and a feasibility study [38].

Figure 1. Zephyr® valve, external view.

Figure 2. Zephyr® valve, internal view. Placed at the orifice of a subsegmental bronchus. On the left, the duckbill valve is closed during inspiration. On the right, it is open during expiration and allows air to escape from the target lobe.

PneumRx (Mountain View, CA, USA) also manufactures a metal ‘‘blocker’’ in nitinol that can retract to cause local collapse. We are not aware of any ongoing clinical trials.

Bronchial fenestration

A method based on the work of Macklem on collateral ventilation was developed by Broncus Incorporated and is designed to alter regional time constants, thus bypassing the diseased airways and reducing lung volume in the affected regions [22,28,37,39]. Treatment with the device requires three procedures. First, an endobronchial Doppler ultrasound of the target region is performed to identify peribronchial vascular structures. Then, using a catheter similar to those used for coronary stenosis dilatation, fenestration (perforation of a bronchus) is performed between a central airway and the target adjacent lung parenchyma. Finally, a drug-eluting stent similar to those used by cardiologists is inserted in the orifice to maintain this fenestration open.

This procedure has been tested in a few patients but to date few data are available in the form of published articles. Studies have been performed on explanted human emphysematous lungs which showed the device could significantly improve expiratory flow [28,40]. It has also been tested in 19 subjects with emphysema, demonstrating immediate improvement in dyspnoea and respiratory function scores (FEV1, FVC, RV) but this improvement was not sustained. These data are only available in the form of abstracts; no data concerning morbidity and mortality for the procedure are available to date [39]. Inclusion in a multicenter randomized double-blind trial involving 315 patients has just ended. The first results should be available early in 2010.

Biological remodeling

The potential advantage of the lobar sealing technique, also called biological lung volume reduction, compared with the endobronchial occlusion devices described above, is being able to circumvent local reinflation due to collateral ventilation of the target lobe. This treatment acts at alveolar rather than bronchial level and has the potential disadvantage of being irreversible. A system using administration of two different substances via a dual lumen catheter passed through the instrument channel of a flexible bronchoscope has been developed by Aeris Therapeutics (Woburn, MA, USA). Animal
Bronchoscopic treatments for emphysema studies have been performed, in particular on a sheep model of emphysema; the procedure was well-tolerated and resulted in local retraction with improvement in ventilatory mechanics [41]. This procedure was subsequently studied in six patients with emphysema, who showed good clinical response and, in principle, an acceptable safety profile [42]. More recently, a phase-2 study involving 50 patients with emphysema showed a significant improvement in FEV1, FVC and RV/TLC ratio 12 weeks after treatment, again with a safety profile that seemed to be acceptable [43]. Larger clinical trials will begin shortly in Europe, in particular in France.

• Current techniques for endoscopic lung volume reduction use two distinct concepts: closure of anatomical airways and creation of extra-anatomical airways.
• Closure of anatomical airways involves blocking the entry of air into a lobe or segment affected by emphysema, using endobronchial blockers, endobronchial valves or biological glues.
• Creating extra-anatomical airways in a lobe affected by emphysema makes possible bypassing of the airways that hinder lung emptying.
• Endobronchial valves prevent air from entering the target area during inspiration and allow it to escape during expiration.
• Bronchial fenestration involves creation of an opening in certain airways.
• During biological remodeling, lobar sealing circumvents local reinflation due to collateral ventilation of the target lobe.

Clinical and physiological response to endoscopic treatment of emphysema

It has been demonstrated that LVRS improves the symptoms of emphysema by providing improved exercise capacity, FEV1 and FVC, as well as reducing residual volume [4,9,10]. However, the data available on endobronchial valves suggest that clinical response to this treatment is variable and inconsistent. In the studies available, the patients treated presented different types of responses. Several patients noted an improvement in dyspnoea as reported on various questionnaires, without any objective improvement in their exercise capacity or respiratory function at rest. It is difficult to distinguish this response from a placebo effect. Another group of patients showed objective improvement in their exercise capacity (6-minute walk distance or exercise test) without change in their ventilatory parameters at rest (spirometry and lung volume measurements). Finally, some patients showed subjective and objective response, both on exertion and at rest, with a significant increase in FEV1 and FVC combined with a reduction in RV and RV/TLC ratio.

The initial study of the first eight patients treated with the Emphasys valve showed improvement in FEV1 of 34% and decrease in RV of 11%, both significant. Lobar collapse was noted in the three patients who showed the greatest improvement in FEV1, whereas the radiographs did not show collapse in the patients who presented less response [31]. Subsequently, other small cohorts have shown variability in the improvement of dyspnoea, FEV1, FVC and exercise capacity in patients treated with endobronchial valves, with patients showing varying degrees of response [29–34]. However, results from the first 98 patients treated with the Emphasys valve showed small but significant improvement in FEV1 of 10.7% ± 26.2% (p = 0.007), in FVC of 9.0 ± 23.9% (p = 0.024), and also in 6-minute walk distance of 23.0 ± 55.3% (p = 0.001) [32]. Again, the subjective clinical response observed was not always related to the physiological improvement measured at rest. A correlation between improvement in symptoms and greater reduction in lung volume, as measured by CT scans before and after treatment, was also demonstrated. However, the study of 57 subjects treated with Spiration endobronchial valves [44] did not find a link between improved respiratory function tests and the presence of collapse on CT scans (Fig. 3).

Hopkinson et al. also observed a significant improvement in exercise capacity in 19 patients who received unilateral endobronchial valve treatment. In their cohort, only five patients showed radiological signs of atelectasis after treatment. They explained this improvement by a reduction in dynamic hyperinflation observed in these subjects; the same phenomenon was observed in patients without radiological collapse. They suggested that interlobar collateral ventilation prevented local collapse, but that if resistance in these collateral ventilation channels was high enough, it could still result in reduction of hyperinflation during exercise [24].

Considering these encouraging first results, the Emphasys valve was the subject of the VENT randomised multicenter study [45]. Standard medical treatment was compared with unilateral implantation of endobronchial valves in 321...
patients with severe heterogeneous emphysema; the randomisation ratio was 2:1 in favour of endobronchial valves. They used a targeting system based on pre-treatment CT scan images to determine the lobe to be treated. The primary outcome measures were improvement in FEV1 and 6-minute walk distance six months after treatment. The study also aimed to establish the safety profile of this treatment. In the group of patients who received endobronchial valves, there was a small but significant improvement of 6.8% in FEV1 ($p = 0.002$) and of 5.8% in 6-minute walk distance ($p = 0.02$). This response was more marked in patients with a high radiological score for emphysema "heterogeneity" before treatment (difference in severity of emphysema between lobes on CT scan); 35.2% patients with heterogeneous emphysema showed improvement of over 15% in FEV1, compared with 12.5% for the control group. The presence of complete fissure of the treated lobe was also predictive of enhanced functional and radiological response, indicating once again the importance of collateral ventilation.

Overall, the use of endobronchial valves appears safe with a mortality rate below 1% and a complications rate between 3 and 17%. The complications observed included: pneumothorax with or without persistent bronchopleural leak, more frequent exacerbations of COPD, respiratory failure post-procedure and pneumonia post-obstruction [29,32,34,38,44]. In the VENT study, the most frequently observed complication was late-onset pneumonia in nine patients (4.2%); none caused death, but three patients required removal of their valves [45]. Some authors have suggested that the occurrence of localized pneumothorax was more related to local collapse rather than iatrogenic injury; the latter was observed in patients who showed significant radiological response and with leakage in the lobe adjacent to the treated lobe [32].

The VENT study results showed a relatively modest benefit, even though it was highly significant when taking into consideration all the patients studied [45]. Unlike LVRS, endoscopic treatment of emphysema did not improve survival in any of the subgroups of patients treated, with a mortality rate similar to valve treatment compared with the control group. Improvement in FEV1 and 6-minute walk distance unfortunately did not follow the "normal" curve in statistical terms. There were clearly responding and non-responding patients. This argument was admittedly understood by the Food and Drug Administration (FDA) that asked Emphasys to conduct a supplementary study to validate factors predictive of response (a difference between emphysema heterogeneity score and interlobe destruction greater than 15%, with complete fissure). The backers of this start-up who had already invested over 90 million dollars in the previous eight years decided to withdraw and not invest a further 12 million dollars in a supplementary study.

Fortunately, the valve affair does not stop here, even though the FDA's decision against marketing approval for the Emphasys valve has by that very fact resulted in cessation of activity for the company that produced Zephyr® valves. The company has been taken over. There are plans to evaluate predicted outcome with pre-treatment (endoscopic) measures of in situ collateral ventilation using a special catheter. This work was validated in 11 patients with emphysema in a recent study and the technique should soon be available in France [46].

**Conclusion**

After smoking cessation and oxygen therapy in hypoxaemic patients, LVRS is the only treatment capable of extending survival in patients with emphysema. Patients able to undergo this surgery and who present emphysema predominant in the upper lobes, low-exercise capacity and carbon monoxide diffusing capacity and FEV1 over 20% should be referred to a thoracic surgeon for an opinion. The development of less invasive therapies to treat severe hyperinflation could possibly change our practice, even though this is not currently the case.

Overall, the response to treatment with endobronchial valves has been less than expected and mainly inconsistent. The presence of collateral ventilation probably has a significant impact on this observed variability in physiological response. Even when attempting to correctly target the lobe to exclude, a large proportion of patients will not develop radiological collapse in the long term [35,36,47]. Studies are underway to test the Spiriration valve as well as bronchial fenestration systems and bronchial remodeling using a biological adhesive. It will be interesting to examine the results of these trials, particularly the last two processes as their mode of action differs from that of endobronchial valves and may help overcome the problem of collateral ventilation.

The future role of endoscopic therapy in emphysema will, in large part, be decided by the results of these studies. These therapies are currently experimental and should be proposed in the context of clinical research to patients who are not candidates for LVRS or who have refused it. Thus, in what we hope will be the near future, the treatment armamentarium for emphysema may be extended allowing endoscopy to play an important role.

**KEY POINTS**

- Lung volume reduction surgery often has a poor risk-benefit ratio.
- The endoscopic techniques are: reduction in the volume of diseased lung (using plugs, one-way valves, or injection of biological adhesive or foam in the parenchyma), and redistribution of ventilatory flow (bronchial fenestration).
- There are two alternatives to lung volume reduction surgery: closure of anatomical airways and creation of extra-anatomic airways.
- Endobronchial valves, bronchial fenestration and biological remodeling are used.

**Disclosure of interest**

The authors declare that they have no conflict of interest concerning this article.
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