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REVIEW ARTICLE

Modern methods for endoscopic treatment of obstructive pulmonary diseases

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Abstract

Background: Despite modern medicine's greatest efforts, many patients suffering from chronic obstructive pulmonary disease (COPD) and asthma remain refractory to the best treatments available. Bronchoscopy is increasingly being used to explore new approaches for treating these diseases, and several new techniques have recently shown encouraging results. The purpose of this review will be to shed some light on these methods.

Methods: We searched Pubmed and Embase for English language articles from 1995 to September 2014, as well as ongoing trials on ClinicalTrials.gov. The following prespecified terms were used to search for clinical trials and case reports from the past 20 years: "endoscopic treatment of COPD", "endobronchial valve", and "bronchial thermoplasty". **Results and discussion:** In search for new COPD treatments, several trials have assessed the efficacy of one-way valves and other conceptually similar techniques including biological sealants and thermal vapor ablation. These methods all operate within a similar paradigm where the intention is to maximize ventilation of the remaining healthy parts of the lung, and to minimize the use and the space occupied by the diseased lung tissue. Similarly, a new non-pharmacologic therapeutic approach in asthma, bronchial thermoplasty (BT), was recently approved for use in the United States for adults with severe disease. The goal is to reduce the mass of hypertrophied smooth muscle in the bronchi to decrease bronchoconstriction. **Conclusion:** Both BT and the bronchoscopic treatments for COPD have shown promising results in recent studies, suggesting the onset of a new direction in obstructive lung disease treatment.

Keywords

Asthma, bronchial thermoplasty, chronic obstructive pulmonary disease, endoscopic treatment, endobronchial valve

History

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Introduction

Obstructive lung diseases are a major cause of morbidity, mortality and financial strain in our modern world. Within this group, asthma and chronic obstructive pulmonary disease (COPD) are two of the most common etiologies. COPD is currently the fourth most common cause of death worldwide, and its mortality rate is expected to continue to increase [1]. Similarly, an estimated 300 million people around the world suffer from asthma, and it is responsible for approximately 1 in every 250 deaths worldwide per year [2]. Current treatments for these diseases have limitations, therefore the search for new methods is the subject of continuous research. Novel advances in bronchoscopic techniques have introduced new possibilities to the realm of management and treatment of both COPD and asthma, and the purpose of the following review will be to shed some light on these new methods.

The disease process in COPD results in airway wall remodeling and emphysema, and a resultant reduction of air flow [1]. Emphysema is defined as a permanent enlargement of the airspaces distal to the terminal bronchioles, and leads to the destruction of the normal alveolar structure and loss of elastic recoil. This process causes air entrapment during exhalation, and hyperinflation, leading to a flattening of the diaphragm and poorer contractility. Physiologically, there is an increase in functional residual capacity (FRC) and a decrease in inspiratory capacity (IC). Clinically, the increased effort required to complete respiration results in pharmacologically refractory dyspnea, necessitating alternate forms of intervention such as the new bronchoscopic techniques discussed below.

Meanwhile, the pathophysiological changes seen in asthma are due to a combination of bronchial hyperresponsiveness, chronic inflammation, and remodeling of the bronchial wall [3]. The process of remodeling is multifaceted, but ultimately results in thickening of the airway wall. This includes deposition of extracellular matrix proteins (ECM) and subepithelial fibrosis; hyperplasia and hypertrophy of airway smooth muscle (ASM), goblet cells, and mucous

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glands; and also neoangiogenesis [4]. One specific feature of airway remodeling, which has been directly implicated in bronchoconstriction, is smooth muscle hypertrophy. Despite the most advanced treatments, 5–10% of asthmatics still have symptoms that are severe and badly controlled – this is known as severe persistent and refractory asthma [5]. And this is the main target population for bronchial thermoplasty.

Methods

In our article we describe and discuss the modern, endoscopic treatments for obstructive pulmonary disease. We searched Pubmed and Embase for English language articles from 1995 to July 2014, as well as ongoing trials related to this topic on ClinicalTrials.gov. The following prespecified terms were used to search for clinical trials and case reports from the past 20 years: “endoscopic treatment of COPD”, “endobronchial valve”, and “bronchial thermoplasty”. Within the relevant articles, we subsequently searched for pertinent references cited in those papers. We found approximately 227 relevant publications and chose those considered to be the most influential and to have the best methodology. Since submitting our original version and receiving our first review, we updated our search in September 2014.

Results and discussion

COPD – surgical treatment of emphysema

Treatment of COPD primarily consists of smoking cessation and pharmacotherapy, however, in patients who have the most severe form of the disease, with predominant emphysema, it is often ineffective [6]. Therefore, surgical methods aimed at lung volume reduction (LVRS – lung volume reduction surgery) were introduced in the treatment of select COPD patients at the end of the twentieth century [7]. During thoracotomy or videothoracoscopy, 20–30% of the most affected areas of lungs are removed, decreasing lung hyperinflation and consequently, improving respiratory muscle function and reducing dyspnea. However, this method can result in several complications, and some patients do not achieve the expected improvement.

In the largest available study, “National Emphysema Treatment Trial” (NETT), the researchers compared surgical and pharmacological treatment. An improved survival rate in the surgical group was observed only in patients presenting with upper lobe predominant emphysema and low exercise tolerance ($RR=0.47$). Conversely, in the other subsets of patients treated surgically, the mortality rate assessed after two years was found to be higher [8]. However, this was mostly driven by a high perioperative mortality rate, which was found to be as high as 5.5%, and was predominantly due to major respiratory and cardiovascular complications (29.8% and 20%, respectively) [9]. Another surgical option for the advanced form of COPD is lung transplantation, however, due to the limited availability of this procedure, it is rarely performed.

Endoscopic treatment of emphysema

Bronchoscopic techniques are rapidly improving, and several new endoscopic treatments for emphysema

(BLVR – Bronchoscopic Lung Volume Reduction) have been recently introduced. The most common method of BLVR involves the implantation of one-way endobronchial valves (EBV), whose purpose is to reduce the air flow to the areas of diseased lung during inhalation. They are placed in the most affected areas of the lung in patients with heterogeneous emphysema, and the valve blocks airflow into the airway distally, but at the same time it allows the air and secretions from the airways distal to the valve to exit. This results in atelectasis of the unventilated lobe [10].

The most commonly used EBV, Zephyr (formerly Pulmonx and Emphasis), has a duck-billed shape, and is coated by a nickel-titanium, self-expanding tubular mesh that is covered with a silicone membrane, allowing for precise adherence to the bronchial wall [11,12]. VENT (Endobronchial Valve for Emphysema Palliation Trial), the largest randomized trial using this type of valve, investigated the safety and effectiveness of this method [13]. A total of 321 patients with severe COPD, aged 40–75 years, with heterogeneous emphysema and FEV1 (Forced Expiratory Volume in one second) values in the range of 15–45% of predicted, were examined. Out of this group, 220 patients were treated with the Zephyr EBV (EBV group), and the others received standard medical care (control group). At six months post-procedure, an average improvement of 6.8% in FEV1, and of 5.8% in the six-minute walk test (6MWT) were observed in the EBV group when compared to the control group. Additionally, an improved quality of life (assessed by St. George’s Respiratory Questionnaire), a decreased feeling of breathlessness, and a reduced number of hours on supplemental oxygen were reported. However, patients treated invasively experienced increased rates of adverse events, such as COPD exacerbations requiring hospitalization, pneumothorax, and hemoptysis. Furthermore, increased incidences of pneumonia (4.2%) in the unventilated parts of the lung were observed. Nevertheless, this study helped identify heterogenous emphysema as a factor present in patients for whom the treatment was most effective. Although the mechanism is not entirely clear, the reduction of the most severely affected lung units likely caused increased ventilation of the less emphysematous parts of the lungs and thereby, improved respiratory parameters. Therefore, an accurate analysis of the tomographic image of the pulmonary parenchyma is recommended before patients are selected for EBV therapy.

In evaluating patients for EBV, the continuity of the interlobular fissure has proven to be an important prognostic factor (in the healthy population, the anatomical variant of incomplete interlobular fissure occurs in 21–31%) [14]. The integrity of the interlobular fissure eliminates disadvantageous collateral ventilation, and provides better isolation of atelectasis in the parts of the lungs closed by the EBV [15,16]. This can be assessed by an endobronchial technique called the Chartis System, which allows precise measurement of air pressure and flow in the lung compartments (lobes and segments), as well as their structural integrity [17,18]. It had an accuracy of 74% in correctly selecting patients who would benefit from EBV treatment. Similarly, high-resolution computed tomography (HRCT) has recently been shown to effectively assess the integrity of interlobular fissures [19].

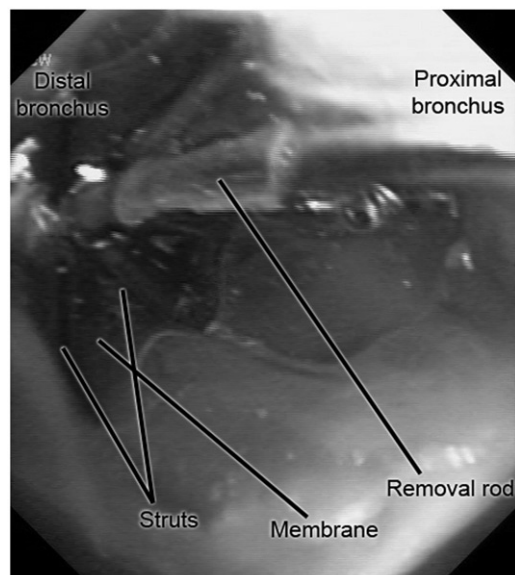


Figure 1. The Spiration intrabronchial valve inside bronchus.

Using a similar mechanism, the Spiration intrabronchial valve (IBV) (Figure 1), is umbrella-shaped, and has distal anchors and proximal struts covered by a synthetic polyurethane polymer, which stabilizes it in the airway [20]. Currently, these valves are primarily used for treating select, prolonged postoperative air leaks [21]. So far, there has only been one randomized trial using this type of valve in patients with COPD. It found no improvement in patients' respiratory parameters, but significant improvement in quality of life was observed [22]. There are currently several studies assessing COPD treatment with IBVs, such as The Spiration Valve System for the Treatment of Severe Emphysema (SVS) and Evaluation of the IBV[®] Valve for Emphysema to Improve Lung Function (EMPROVE), which are scheduled for completion in 2015, so there should be a clear understanding of their role in the treatment of severe emphysema in COPD soon.

There are other methods of endoscopic lung volume reduction, however, either their clinical usefulness is limited, or research on their use is still in the initial phase. Notable among them, is stent-supported airway bypass. This procedure is performed under general anesthesia, and it creates artificial pathways through the walls of bronchi (fenestrations) into the surrounding parenchyma, allowing the air trapped in the lungs to escape. At the same time, the fenestrations decrease the flow through collapsed and affected end sections of bronchi with high resistance (in the emphysematous parts of the lung, these act as one-sided valves preventing air escape). The stents that are implanted into the bronchi release paclitaxel, preventing overgrowth by fibrous tissue. This leads to improved expiratory flow, reduced residual volume (RV), and improved respiratory mechanics [23,24]. However, the observed initial improvement in respiratory parameters after airway bypass is short-lived, as was demonstrated by the EASE study. After 6 months, despite transient improvement, no sustainable benefit, such as improved FVC, was noted in the study group when compared to the control

group [25]. Given the absence of any durable benefit associated with airway bypass, this treatment is currently not recommended.

Thermal vapor ablation is another promising method. This treatment causes inflammation in the airway, leading to a reduction in the volume of the emphysematous lobe [26,27]. Biologic lung volume reduction (BioLVR) involves an intrabronchial administration of fibrin-based hydrogel, which causes localised scarring and contraction of the bronchial wall, leading to the ventilation exclusion of damaged areas of the lung. Preliminary data suggest this may be a safe and effective therapy for patients with advanced homogenous emphysema, unlike the Zephyr valve, which has shown benefit in predominantly heterogeneous emphysema [28].

A novel, experimental method is a self-expanding endobronchial occluder (SEEO). It is made of nitinol wire mesh, filled with several fibre layers, and uses three collars to maintain its position in the airway. It is placed bronchoscopically into the segmental or subsegmental bronchi, and blocks the air flow as the collars push out against the bronchi wall. After 3 months, an improvement in quality of life (SGRQ) and in pulmonary function (increase in FEV1 of more than 15% compared to pre-treatment FEV1 in 78% of patients) was recorded. However, this improvement was substantially decreased in the long-term 36 month follow-up. Despite the apparent ease and safety of this technique, current data show a long-term benefit in only a minority of patients who received the treatment, suggesting there is little overall advantage to using this method [29].

Another method of BLVR is the lung volume reduction coil (LVR-coil). The LVR-coil consists of Nitinol wire, and is made in a range of lengths (70–200 mm) to accommodate airways of different sizes. Under general anesthesia, it is delivered by a catheter into subsegmental bronchi, and the position is determined by fluoroscopy. Once ejected, the coil assumes its shape and compresses the lung parenchyma [30]. In the largest LVR-coil study to date, 60 patients in 11 European hospitals took part in a prospective, cohort, open-label multicentre feasibility study [31]. Patients with COPD and either upper or lower lobe predominant bilateral heterogeneous emphysema were included in the study, and they were treated with an average of 10 (range 5–15) coils per lobe. In 115 procedures, there were no serious periprocedural adverse events, although some adverse events were recorded in the follow-up (e.g. within 30 days post-treatment 6.1% of patients experienced COPD exacerbations, 5.2 % experienced pneumonia, and 3.5% experienced a pneumothorax). Not only do the results suggest that the procedure is clinically safe, but follow-up at 6 and 12 months also showed significant clinical improvements. The observed change at 6 and 12 months (all $p < 0.01$) in FEV1 was $+0.11 \pm 0.20$ L and $+0.11 \pm 0.30$ L, in RV was -0.65 ± 0.90 L and -0.71 ± 0.81 L, in SGRQ was -12.1 ± 12.9 and -11.1 ± 13.3 points, and in the 6MWD was $+29.7 \pm 74.1$ m and $+51.4 \pm 76$ m, respectively. However, 25 patients (42%) exited the study after 6 months, due to differing national ethics committee requirements, decreasing the quality of the 1-year follow-up. Nonetheless, this study suggests that the procedure is safe and will result in clinical improvement.

Evaluation of the usefulness of these methods in the treatment of emphysema requires further randomized studies on a larger group of patients. The greatest clinical effect appears to be obtained with the Zephyr valves in patients with heterogenous emphysema and continuity of the interlobular fissure (33%), and its efficacy is supported by the most robust clinical data. Preliminary results of the LVR-coil are showing its effectiveness in both heterogenous and homogenous emphysema, regardless of interlobular ventilation. But more long-term randomized trials are needed to confirm their efficacy. Meanwhile, biological sealants and thermal vapor ablation are now in clinical trials and are emerging as potential alternatives for treating severe emphysema with concomitant interlobular ventilation. Stent-supported fenestrations with airway bypass is a complex technique with an increased risk and no long-lasting benefit and consequently, has not been approved [32]. More studies of BLVR are needed to enable us to better identify the subset of patients who will gain the greatest benefit from each treatment.

Bronchial thermoplasty

Bronchial thermoplasty (BT) is a new endoscopic therapeutic option approved by the U.S. Food and Drug Administration (FDA) in 2010 for patients with severe persistent asthma, whose symptoms are uncontrolled despite maximal pharmacotherapy. The aim of this method is to reduce the mass of smooth muscle in the bronchi and thereby, decrease bronchoconstriction [33]. This is achieved through the use of radiofrequency waves, which induce a controlled local heating effect (65 °C), and can be performed under local or general anesthesia. By using a catheter with a basket carrying four expandable electrodes, thermal energy is applied to bronchi with a 3–10 mm diameter, and ablations of short 5 mm sections are carried out (Figure 2). To minimize complications, BT is typically performed in three sessions separated by three-week intervals. It is performed in the entire bronchial tree except the right middle lobe bronchus, to prevent atelectasis. Bronchi of the right lower lobe are treated in the first session, followed by the bronchi of the left lower lobe and finally, in the last session the bronchi of both upper lobes are treated. One procedure usually takes 30–60 minutes [34].

The first study to include patients with asthma was published by Cox et al. [35] in 2006. It included 16 patients with mild to moderate asthma (forced expiratory volume in one second, FEV₁, > 80%), and evaluated the safety, airway

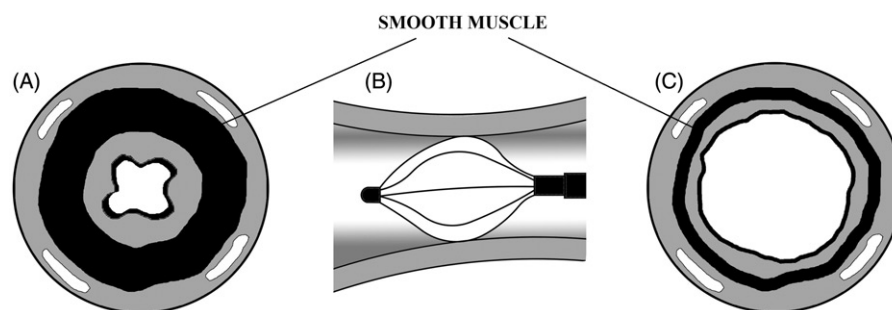
hyperresponsiveness (AHR), and lung function during the 2 years following BT. In the study group, they reported a statistically and clinically significant improvement in AHR that persisted through the two-year follow-up period. At 12 weeks and 1 year, an increase in prebronchodilator FEV₁ (% predicted) was observed; however, no significant change from baseline in prebronchodilator and postbronchodilator FEV₁ (% predicted) at the 2-year follow-up was reported. This research showed that BT was tolerated well by patients with asthma, and that there were no serious adverse events related to the procedure. Limitations of this study included the lack of a control group and a small number of subjects. These encouraging results led the way for subsequent multicenter, controlled studies seeking to assess the effectiveness of BT.

A multicenter, randomized study, AIR [36] (Asthma Intervention Research), recruited 112 patients with moderate to severe asthma, classified according to the GINA criteria. The main objective of the study was to evaluate the frequency of mild exacerbations in the two-week period of abstinence from β_2 -agonists at 3, 6 and 12 months after BT. The results indicate that the BT group experienced approximately 10 fewer mild exacerbations per subject per year in comparison to the control group. Furthermore, the BT group reported a greater number of symptom-free days, reduced use of rescue medication, and an improvement in morning peak expiratory flow (PEF), in quality of life measured by AQLQ (Asthma Quality of Life Questionnaire), and in asthma control (ACQS, Asthma Control Questionnaire scores). There were no significant differences between the groups in FEV₁ measurements, nor in AHR.

A subsequent randomized study, RISA [37] (Research in Severe Asthma), was performed to assess the safety and efficacy of BT in 32 patients with severe asthma. Following BT, the study was divided into several phases of incrementally reduced corticosteroid use. At 22 weeks, the BT group showed an improvement in FEV₁ (% predicted), better control of asthma, less use of rescue medication, and far more patients were able to reduce their dose of ICS and withdraw oral corticosteroids when compared to the control group. However, the interpretation of subjective improvement (AQLQ, ACQS) in both of these studies (AIR, RISA) is limited by the lack of patient blinding, and the potential placebo effect of BT.

The largest multicenter, randomized, double-blind, sham-controlled, clinical trial, AIR 2, (Asthma Intervention Research 2) [38] enrolled 288 patients with severe, uncontrolled asthma refractory to high dose ICS and long-acting

Figure 2. (A) Cross section of a bronchus in a patient with severe asthma before bronchial thermoplasty treatment; note the hypertrophied smooth muscle and small airway diameter. (B) Catheter in the airway with opened electrode basket. (C) Cross section of a bronchus in a patient with severe asthma after bronchial thermoplasty treatment; note the decrease in smooth muscle and increased airway diameter.



β 2-agonists. All patients underwent three bronchoscopies performed 3 weeks apart. The study evaluated the efficacy and safety of BT, and changes in quality of life compared to a baseline assessed by the AQLQ at 6, 9 and 12 months after the procedure. A blinded assessment team conducted all follow-ups. The study showed that the possibility of improving the quality of life by at least 0.5 points, the minimum considered to be significant for patients, was greater in the group treated with BT (79%) compared to patients who underwent a sham intervention (64%). The BT group, when compared to the sham-control group, also demonstrated a decreased frequency of severe asthma exacerbations (by 32%), a decreased incidence of hospitalization (by 73%), a decreased number of medical visits (by 84%), and a reduced number of days absent from work/school (by 66%). Sixteen patients from the BT group and 2 patients from the control group were hospitalized during the 6 weeks following bronchoscopy because of adverse events. All side effects were resolved by standard therapy, except hemoptysis, which occurred in one patient after BT and required embolization of the bronchial artery. It appears that the benefits of BT in patients with severe, uncontrolled asthma outweigh the short-term, increased risk of adverse effects.

There are already results from a five-year follow-up of patients after treatment with BT. The method has proven to be safe, and no deterioration in lung function (FEV1, FVC – Forced Vital Capacity) has been observed. Furthermore, there were no severe complications such as pneumothorax, need for intubation, mechanical ventilation, cardiac arrhythmias, or death resulting from the procedure [39–41]. Additionally, 93 high-resolution computed tomography (HRCT) pairs from the AIR 2 group were evaluated at year 5, and there were no findings of new, abnormal structural changes in the airways, such as bronchial stricture, bronchiolitis obliterans, or new pulmonary emphysema (compared to previous HRCT), that could have resulted from the procedure [41].

Many aspects of BT are still controversial, including how to select the location for treatment. The inflammatory process in asthma primarily affects medium and small calibre bronchi, however the catheter and the basket used in BT cannot be introduced into a bronchi with a diameter smaller than 3 mm. Furthermore, we still do not fully understand the exact mode of action of BT, such as the role of apoptosis, autophagocytosis, and the effect on fibroblasts and nerve fibers. Therefore, it would be interesting to perform histological analysis of biopsies, and to examine gene expression and the inflammatory markers in sampled tissue following BT. Additionally, a very important and still unresolved issue is the need to identify how to qualify patients for treatment. Currently, the severity of asthma, the frequency of exacerbations, and the dose of inhaled steroids have been taken into account. However, it seems that the assessment of bronchial wall thickness in chest CT scans and especially the indirect measurement of the thickness of the muscle layer in the endobronchial ultrasound can play an important role in the future to help qualify patients for treatment.

In summary, these studies suggest that BT is a promising and safe method that can be used in the treatment of severe asthma. According to the recommendation of GINA (Global Initiative for Asthma, evidence B), BT may be a new

therapeutic option in some countries in adult patients, whose asthma is refractory despite maximal pharmacotherapy [31]. Currently, it is not known how long the beneficial effect of BT lasts and whether there is a need to subsequently repeat the procedure. Therefore, further studies are needed to assess its long-term (longer than 5 years) efficacy and its safety. Furthermore, there is a need for further research to guide selection of patients who will be more likely to benefit from the use of BT, and to develop objective methods for evaluating the effectiveness of the treatment. It is therefore still considered in the joint ERS/ATS guidelines as an experimental therapy that may be used only in patients with severe asthma [42].

Conclusion

Analysis of these new methods for the treatment of COPD and asthma are encouraging for certain patient subsets. The Zephyr valve currently demonstrates the greatest clinical benefit in COPD patients with heterogenous emphysema, the LVR-coil is emerging as a potential therapy for patients with both heterogenous and homogenous emphysema. Stent-supported fenestrations with airway bypass carries high peri-operative risk with no long-lasting benefit, therefore should not be considered as a treatment option. Other techniques, such as IBV, biological sealants, and thermal vapor ablation could prove efficacious as well, but the results from ongoing clinical trials are necessary to properly evaluate them. Similarly, BT is proving to be a viable alternative for treating asthmatics refractory to standard pharmacotherapy. Nevertheless, more randomized, multicentre, blinded studies are needed to clarify what techniques will be most useful, what the long-term effects are, and which patients will benefit most.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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