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Review Article

Up to Date Bronchoscopic Treatment of COPD

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Abstract

Recently emerging techniques have been evolved to treat patients with chronic obstructive pulmonary disease (COPD). Bronchoscopic lung volume reduction for advanced emphysema had proved its efficacy to treat the problem of lung hyperinflation and its consequences in this group of patients, in the same time there was less complications compared to surgical lung volume reduction. During the last few months, a novel bronchoscopic treatment for chronic bronchitis patients has been introduced as the first in human trial. Up to date techniques used for bronchoscopic treatment of emphysema and chronic bronchitis will be discussed in this review.

Keywords: *Bronchoscopy; BLVR; COPD; Emphysema; Chronic Bronchitis*

Abbreviations

BioLVR: Biological Lung Volume Reduction; BLVR: Bronchoscopic Lung Volume Reduction; BTVA: Bronchoscopic Thermal Vapor Ablation; COPD: Chronic Obstructive Pulmonary Disease; CP: Collapse Phenomenon; CT: Computerized Tomography; CV: Collateral Ventilation; CV+: Positive Collateral Ventilation; CV-: Negative Collateral Ventilation; EBV: Endo Bronchial Valves; HRCT: High Resolution Computerizes Tomography; IBV: Intra Bronchial Valves; LVRC: Lung Volume Reduction Coil; LVRS: Lung Volume Reduction Surgery; PLVR: Polymeric Lung Volume Reduction; RF: Radio Frequency; TEV: Total Exhaled Volume; TLD: Targeted Lung Denervation

Introduction

Bronchoscopic techniques for the management of emphysema have evolved from the success of surgical treatment. Lung volume reduction surgery (LVRS) involves the removal of 20% to 30% of each lung and targets the most emphysematous segments. On the other hand, the increased short-term mortality of approximately 5% and postoperative morbidity represented major limitations of surgical lung volume reduction [1]. The reported rate of intraoperative complications is 9% and postoperative complications is 58.7% with elevated risks for reintubation (21.8%), arrythmias (18.6%), pneumonia (18.2%), readmission to the intensive care unit (11.7%) and tracheotomy (8.2%) [2]. Air leaks of a median duration of 7 days have also been reported in up to 90% of patients [3].

In the National Emphysema Treatment Trial (NETT) study, up to 28% of patients were hospitalized or living in a nursing home/rehabilitation facility at 1 month after surgery. Unfortunately, the price of all this postoperative morbidity and mortality does not guarantee benefits. Only 30% of patients in the most favorable subgroup of COPD with upper lobe disease and low baseline exercise tolerance derived a clinically significant improvement in exercise capacity of more than 10 watts and 48% registered a greater than 8-point decrease in the St. George's Respiratory Questionnaire at 24 months [1]. The extremely restrictive selection criteria coupled with the relatively high morbidity have been the likely reasons for the decrease in patients undergoing surgical lung volume reduction since the publication of the NETT data [4].

In the last few years minimally invasive techniques have been evaluated as a method to reduce lung volume in patients with advanced emphysema without exposing them to open thoracotomy. Different Bronchoscopic lung volume reduction (BLVR) systems are undergoing evaluation to achieve benefits of LVRS without the concomitant surgical morbidity [5]. Interestingly, this year a novel bronchoscopic treatment for chronic bronchitis has been introduced as the first in human trials.

In this review, different bronchoscopic modalities for treatment of emphysema and chronic bronchitis will be discussed.

Mechanism of action

Bronchoscopic treatment of emphysema (BLVR): The underlying mechanism for techniques of BLVR would be either:

1. Bypass the obstructed small airways by creating collateral (exo-anatomical) routes of ventilation, which could decrease air trapping and expiratory flow limitation [6].

2. Decrease lung volume by causing atelectasis of the most diseased part of the lungs, by either the use of endobronchial blocker, one way valves, coils, injection of biological sealants which would fill the alveoli or the use of thermal vapor ablation, all aiming at results similar to those of LVRS [6].

3. Radiofrequency ablation of parasympathetic nerve supply of the main bronchi (Targeted Lung Denervation) [7].

Bronchoscopic treatment of chronic bronchitis (Bronchial Rheoplasty): A novel technique for bronchoscopic treatment of chronic bronchitis. The underlying mechanism of action is ablation of mucus-producing airway cells by Pulsed Electric Fields that are delivered to the airways via an endobronchial catheter [8].

(A) Techniques of BLVR

To get the most beneficial outcome of BLVR, precise patient selection is crucial [9]. BLVR can be divided into interventions targeting heterogeneous emphysema and those designed for homogenous disease depending on the Computerized Tomography (CT) morphology of the emphysema subtype [10].

1. Endobronchial blockers

Endobronchial blockers result in resorption atelectasis by occluding airways leading to the targeted lung segments. Initially silicone vascular balloons filled with radio opaque contrast were used (Figure 1). Then the advent of custom built stainless steel stents with a central occlusive sponge has emerged. But, the occurrence of high rate of endobronchial blocker migration, post-obstructive pneumonia, and the need for repeat endoscopic procedures have limited further development of this technique [11].

Figure 1: *Watanabe spigot and example of an endobronchial blocker.*

2. Bronchial valve implantation

In general, two different kinds of valves have been studied for BLVR. The first valves available for clinical evaluation were the endobronchial valves (EBV; Zephyr; Pulmonx, Inc., Palo Alto, California, USA). The EBV has a design similar to a bronchial stent, with a self-expanding, membrane-covered retainer that provides stability and prevents dislocation (Figure 2). Different sizes of EBV are: (4 mm in diameter [in two different lengths] and 5.5 mm in diameter) [9].

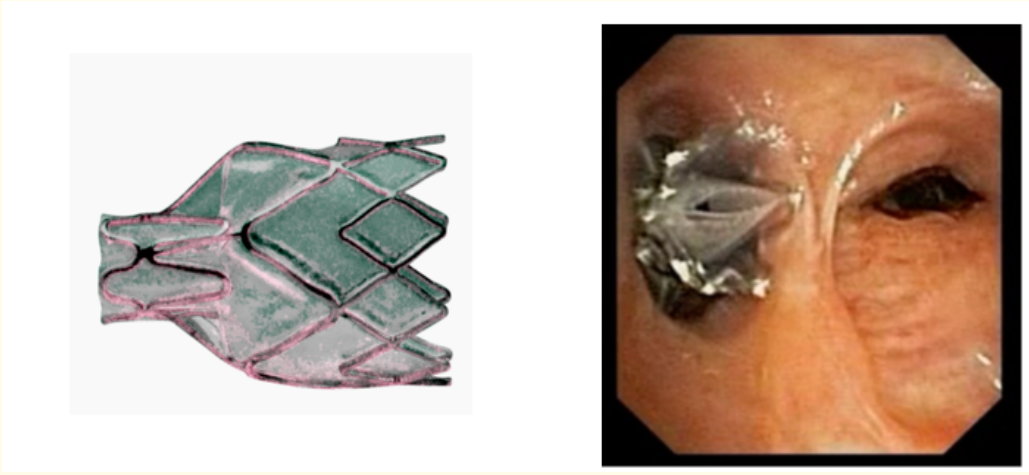

Figure 2: *Endobronchial valve (EBV; Zephyr; Pulmonx, Inc., Palo Alto, California, USA).*

The other one is the intrabronchial valves (IBV; Spiration; Olympus, Tokyo, Japan). The IBV is an umbrella-shaped, one-way valve incorporating a nitinol skeleton consisting of five distal anchors holding the valve in place and six proximal struts covered by a polymer membrane (Figure 3). There are three sizes of IBV (5 mm, 6 mm and 7 mm in diameter) [9].

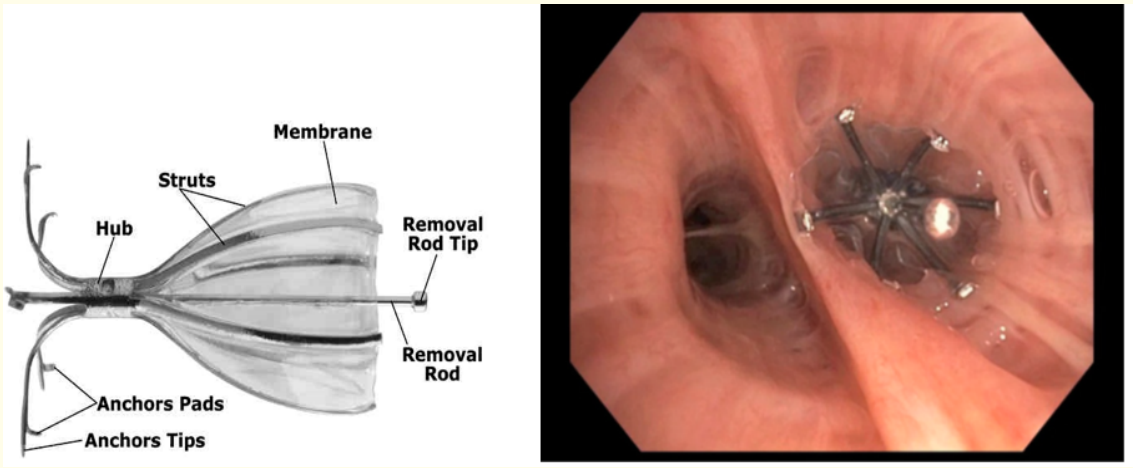

Figure 3: *Intrabronchial valve (IBV; Spiration; Olympus, Tokyo, Japan).*

Both the EBV and the IBV act as one way valves. During expiration, the valves allow the air to exit the targeted area while preventing air from entering the lung compartment during inspiration (Figure 4). Ideally, a reduction of hyperinflation of the most destroyed emphysematous lung parenchyma can be achieved, leading to reduction in target lung volume. Both valves allow mucus to be expelled to prevent post-obstructive infectious complications [9].

Figure 4: *Mechanism of action of IBV: The IBV allows air and secretions to escape naturally along the bronchial wall during expiration.*

Technique consideration

It was proven that fissure completeness between the targeted lobe and the adjacent one, correlates with the magnitude of lobar volume change after valve implantation. Attention to fissure completeness should allow improved patient selection and targeting to minimize the mitigating effects of collateral flow on the clinical response to endobronchial valve therapy [5]. Studies on excised human lungs identified major defects in interlobar fissures in 21 - 30% of oblique fissures and up to 88% of right horizontal fissures [12]. In contrast to normal human lung, resistance across these collateral channels in emphysema is low relative to airway resistance [13].

Techniques for assessment of fissure completeness [9]:

(1) High resolution computerizes tomography (HRCT): complete interlobar fissure is defined as ≥ 90% completeness of the fissure between the target and adjacent lobes on at least one axis in the thin-slice HRCT.

(2) Chartis Pulmonary Assessment System (Pulmonx Inc., Redwood City, California, USA) (Figure 5).

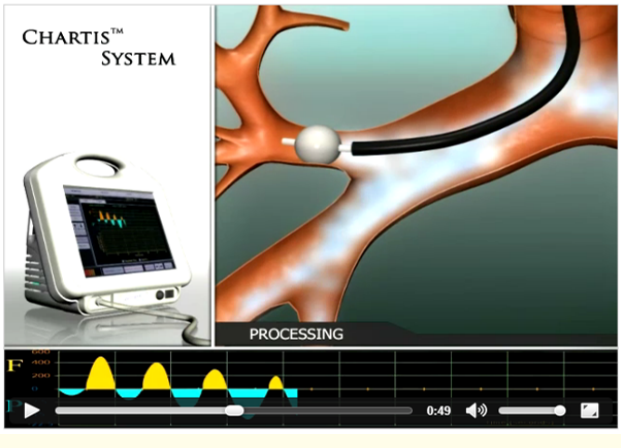

Figure 5: *Chartis Pulmonary Assessment System (Pulmonx Inc., Redwood City, CA).*

The Chartis device is used to bronchoscopically quantify the resistance of airflow through collateral ventilation (CV) by temporarily occluding a lung compartment and measuring the air pressure and flow from the sealed compartment. This measurement allows classifying the patient as "CV negative" in case of low or absent CV or as "CV positive" in case of high CV (Figure 6) [9].

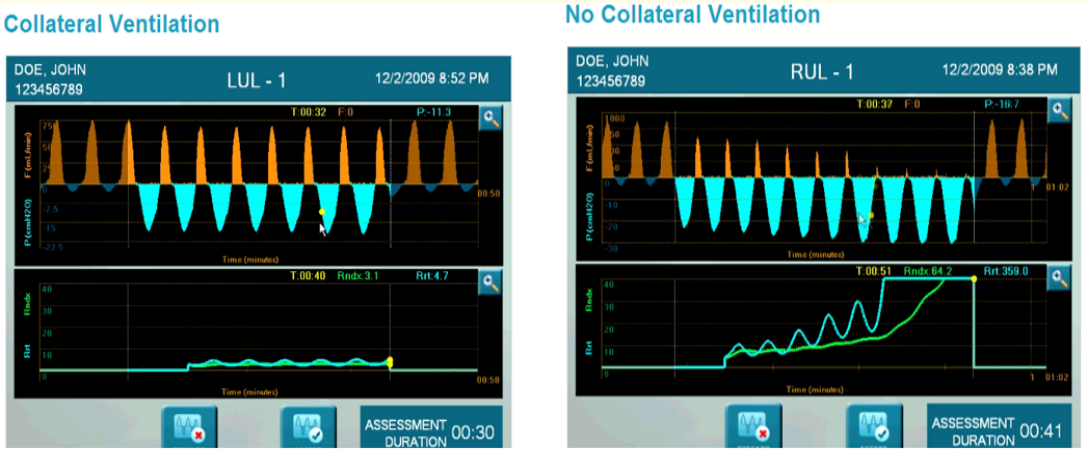

Figure 6: *Chartis system waveform. Left panel demonstrates continuation of airflow after inflation of the balloon confirming the presence of collateral ventilation. On the right panel there is cessation of airflow, confirming absence of collateral ventilation.*

Moreover, Gesierich., *et al.* [14] had introduced Definition of different Chartis phenotypes as presented in table 1.

Table 1: *Definition of different Chartis phenotypes.*

Chartis phenotype	Criteria
CV+	Persistent airflow and: • Flow time ≥ 5 min or • TEV ≥ 1L
CV–	Gradual decrease and termination of airflow and: • Flow time ≥ 1 min and • TEV ≥ 50 mL
CP	Reproducible sudden termination of airflow and: • Flow time < 1 min or • TEV < 50 mL
Unclear	Not fitting in other categories

CV+: Positive Collateral Ventilation; CV–: Negative Collateral Ventilation; CP: Collapse Phenomenon; TEV: Total Exhaled Volume.

Both CT fissure analysis and implementation of the Chartis system appear to optimize patient selection for valve treatment. The results of one retrospective analysis confirmed that the two techniques are comparable and that both offer an efficient method for predicting target lobe volume reduction with valve treatment [15].

Advantage

(1) Effective treatment option for patients with severe heterogeneous upper or lower lobe predominant emphysema [16].

(2) Reversible technique [9].

Hazards

(1) Valve failure due to incomplete fissure and high interlobar CV [17].

(2) Pneumothorax, which is believed to be secondary to parenchymal rupture in the adjacent untreated lung lobe in the setting of rapid volume reduction in the treated lobe. The incidence of pneumothorax following valve placement is variable in different studies, an incidence rate of 30% has been reported [17].

(3) Post-obstructive pneumonia [11,18].

(4) COPD exacerbations (5% to 20%) [19].

(5) High cost that approximate 1,500 Euros per device [9].

3. Coil implantation

It is a technique that is not based on blocking the airways. The lung volume reduction coil (LVRC) (PneumRx, Inc., Mountain View, California, USA) (Figure 7) is composed of nitinol wire [9].

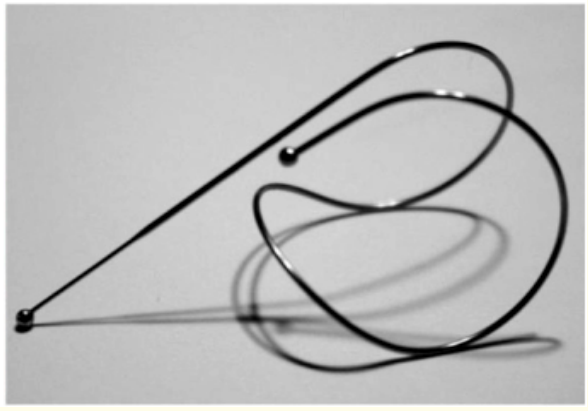

Figure 7: *RePneu Coil (PneumRx, Inc., Mountain View, CA).*

On coil deployment, the straightened coil then conforms to its predetermined shape. By deploying the coil, bends in the airway from the deployed coil result in compression of adjacent lung tissue, creating local lung volume reduction in addition to restoring elastic recoil of the healthier lung compartments. The coils may potentially be adjusted or removed at the time of the procedure [10].

By implantation of up to 10 coils in the targeted lung lobe, volume reduction can be achieved (Figure 8), leading to improvement in respiratory mechanics [9].

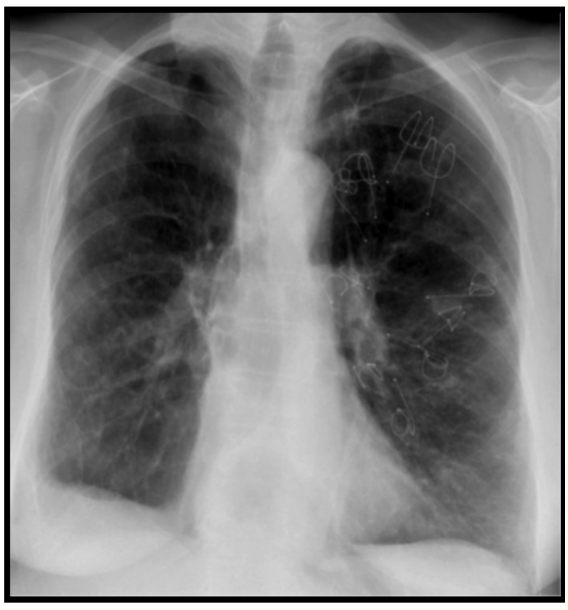

Figure 8: *Chest X-ray after implantation of lung volume reduction coils in the left upper lobe.*

Advantages

(1) No serious adverse events.

(2) LVRC have been shown to be an effective treatment modality in patients with upper and lower lobe predominant emphysema [20].

(3) The success of the procedure is independent from the presence or absence of interlobar CV [21].

Disadvantages

(1) Mild hemoptysis, transient chest pain, COPD exacerbation, pneumonia, and pneumothorax were documented as adverse events [22].

(2) The treatment with coils is a partially irreversible therapy, thus presenting a disadvantage compared with reversible valve implantation [9].

(3) Cost 1,000 Euros per device [9].

(4) Concerns remain that the coils by distorting bronchi will cause bronchiectasis and by kinking pulmonary vessels will cause pulmonary infarcts [11].

4. Airway Bypass Stents

The airway bypass procedure was developed to address the challenges of endoscopic treatment of homogenous emphysema. This was showed in a human ex vivo model in 2003 at Washington University of St. Louis that by creating artificial communications through bronchial walls into the parenchyma of explanted lungs (airway bypass); there was a decrease in the amount of gas trapping and an increased rate and volume of expelled air during forced expirations. The results showed that airway bypass improved the mechanics of breathing in severely emphysematous lungs in vitro. In human clinical trials of airway bypass, anatomic fenestrations were created between the bronchial tree and lung parenchyma aiming to improve decompression of hyperinflated lung [23].

Procedure and mechanism of action [10]

There are 3 steps that are performed via flexible bronchoscopy:

(1) Identification of an area of the segmental bronchi that is free from blood vessels using a doppler probe.

(2) Fenestrating the segmental or sub-segmental airway wall with a needle and balloon dilation.

(3) Placement of a paclitaxel eluting stent (5.3-mm outer diameter, 2-mm length, 3.3-mm inner diameter) (Figure 9). The stent is placed across the airway wall into the emphysematous lung parenchyma. The stainless steel stents is coated with paclitaxel-covered silicone to inhibit granulation and fibrotic tissue from obstructing patency of the fenestrations. The fenestrated passages take advantage of the collateral ventilation seen in emphysema by increasing gas flow from hyperinflated lung parenchyma directly into the main airway during exhalation, reducing hyperinflation.

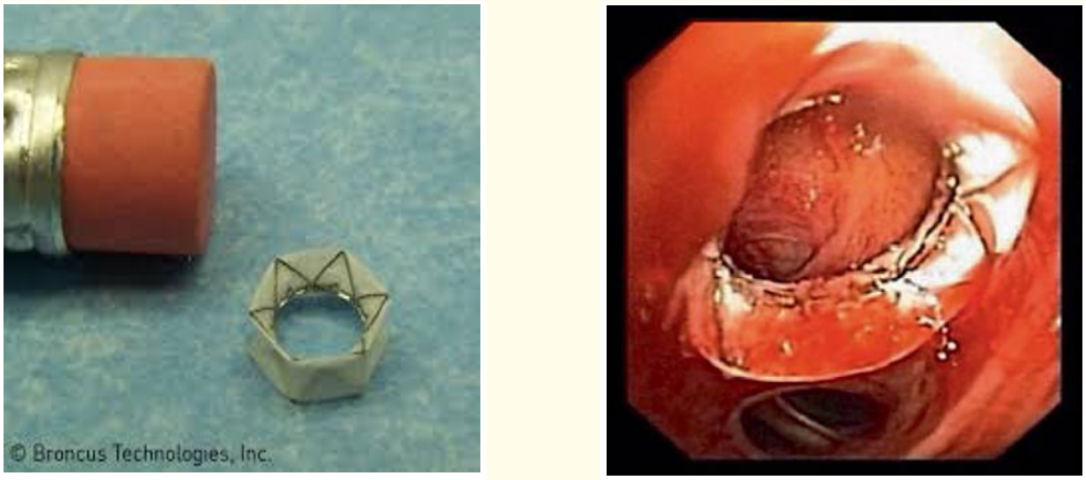

Figure 9: *Airway bypass stent. Left image shows the paclitaxel eluting stent. The right image shows the bronchial airway bypass system placed in the right lower lobe.*

Advantage [9]

Good approach to the reduction of lung volume in patients with advanced homogeneous emphysema by creating new extra-anatomic airway bypasses.

Disadvantage

(1) Need preprocedural confirmation of an avascular location via the doppler probe, to avoid puncturing blood vessels [9].

(2) Stent occlusion by granulation tissue (despite drug elution) [9].

(3) Stent loss [9].

(4) One periprocedural death occurred in a patient in the airway bypass arm due to a ruptured aortic aneurysm [24].

(5) COPD exacerbation, pneumothorax, and pulmonary infection [9].

(6) There is no sustainable benefit could be demonstrated with this technology for airway bypass. Therefore, it is no longer performed in patients with emphysema in Europe [25].

5. Bronchoscopic thermal vapor ablation

Bronchoscopic Thermal Vapor Ablation (BTVA) (Uptake Medical, Seattle, Washington, USA) (Figure 10) is a minimally invasive bronchoscopic treatment that uses heated water vapor delivered to emphysematous lung parenchyma within a targeted region. The vapor induces an inflammatory reaction with subsequent fibrosis, resulting in lung volume reduction within 8 to 12 weeks [9].

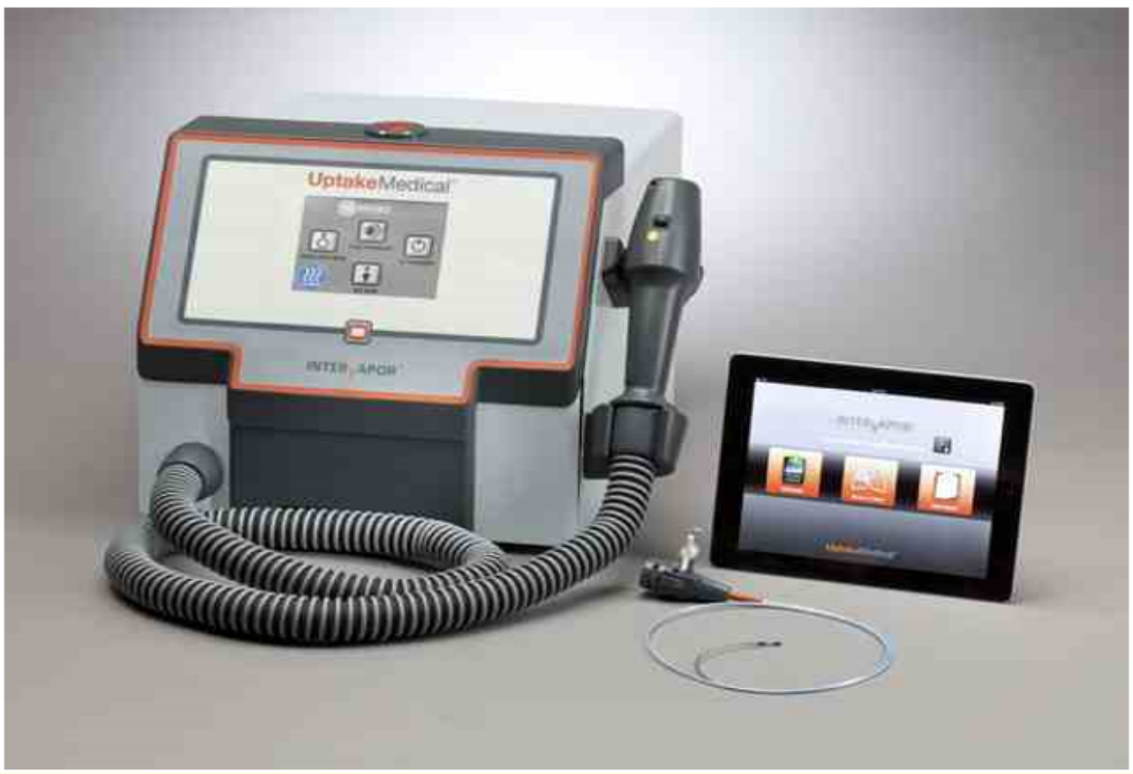

Figure 10: *Bronchoscopic Thermal Vapor Ablation (BTVA) (Uptake Medical, Seattle, WA).*

Procedure

A disposable 2 mm vapor catheter is inserted via flexible bronchoscope to the targeted airways. On the vapor catheter, there is a distal occlusion balloon which isolates the lung segment (Figure 11). An accurate dose of steam generated by an electronically controlled pressure vessel is then introduced to the isolated airways [27].

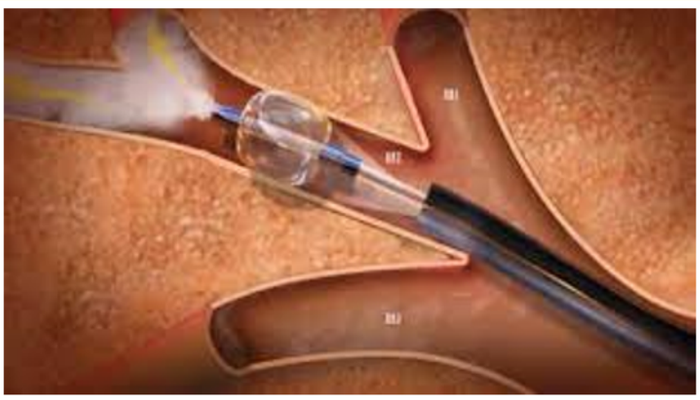

Figure 11: *Vapor catheter, with inflated balloon that isolates the targeted lung segment.*

Mechanism of action

Delivery of thermal energy or heat causes acute tissue injury, which then induces tissue repair with subsequent fibrosis resulting in reductions in volume. The delivery of the thermal dose (together with modifications in the vapor temperatures and/or vapor application times) can also result in complete cell death and initiation of a healing process with new fibroblast growth and collagen deposition, all of which can induce the histological changes necessary to induce BTVA [5].

BTVA creates space in the thoracic cavity by reducing lung size, and so the remaining lung and surrounding muscles (intercostals and diaphragm) are able to work more efficiently [28].

Advantages [11]:

(1) No prosthesis needs to be inserted

(2) It doesn't depend on presence or absence of collateral ventilation

Disadvantages:

(1) COPD exacerbations and Pneumonitis [27].

(2) Lower respiratory tract infections. Patients experienced a flu-like reaction with fever, cough, sputum, dyspnea, and hemoptysis [29].

(3) Cost: 6,000 to 8,000 Euros [9].

6. Biological lung volume reduction

It is a novel endobronchial therapy for emphysema that uses biological agents, as biodegradable substances, blood patches and fibrin plugs to achieve lung volume reduction [10].

Mechanism of action

The rapidly polymerizing sealant is proposed to work at the alveolar level rather than in the airways. The mechanism of action involves resorption atelectasis from airway occlusion, subsequent airspace inflammation, and then remodeling. This remodeling will lead to scarring resulting in contraction of lung parenchyma, and functional lung volume reduction can be expected within six to eight weeks [30].

The sealant causes blockage of inter-alveolar as well as bronchiolar-alveolar collateral channels and abolish the effects of collateral ventilation [31].

Biological lung volume reduction (BioLVR) uses a biological hydrogel involving animal and human products. It is formed of fibrinogen biopharmaceutical suspension and thrombin solution, which polymerize to a hydrogel in situ as they come in contact with each other [10].

The first study related to BioLVR was a safety trial by Reilly and colleagues in 2007 [30], in which there was better clinical outcome with increased dose of the sealant. Further Phase II study confirmed the same finding was performed [32,33].

After completion of these Phase II studies, BioLVR was replaced by polymeric lung volume reduction (PLVR). PLVR is similar to BioLVR but differs only in the reagent used to induce the inflammatory response. PLVR uses synthetic hydrogel foam called AeriSeal system [34-36].

An interesting parallel development has been the bronchoscopic injection of autologous blood and fibrinogen into an emphysematous bulla to affect similar volume reduction [37]. Injection of autologous blood can improve pulmonary function, exercise tolerance, and quality of life and may produce benefits as a palliative treatment in patients with very severe COPD [38]. A pilot study reported in 2016 assessed the efficacy and safety of BLVR using low-cost agents including autologous blood and fibrin glue [39], this biological lung volume

reduction treatment is promising in terms of its low-cost. Notably, however, the study had very small sample size and short follow-up. There is a need for long-term studies of cost, effectiveness, and safety in relation to this method.

Advantages [10]:

(1) The biological agent functions well despite collateral ventilation.

(2) The technique would not have the associated complications of a foreign body (i.e., valves or stents).

Disadvantages:

(1) COPD exacerbations with rates similar to that reported with other procedures [10].

(2) Irreversible technique and long-term follow up data is critical. Atelectasis may diminish with time because of biodegradation of the hydrogel [40].

(3) High cost of PLVR that uses the AeriSeal system 6000 - 8000 Euros [9].

7. Targeted Lung denervation [41]

Targeted lung denervation (TLD) is a novel bronchoscopic therapy for COPD which ablates parasympathetic pulmonary nerves running along the outside of the two main bronchi with the intent of inducing permanent bronchodilation.

TLD was delivered via a dual cooled radiofrequency (RF) generator system (Figure 12). As RF current is delivered through the airway and surrounding tissues, these tissues are heated and the nerves are ablated. Simultaneous cooling removes heat from the inner surface of the bronchi. The net effect is the targeted tissue ablation at depth with minimal heating and damage of the inner surface of the airway. The goal of targeted ablation is to disrupt motor axons within bronchial nerve branches running along the main bronchi, thereby blocking parasympathetic signaling to the lungs and decreasing neuronal release of acetylcholine (Figure 13).

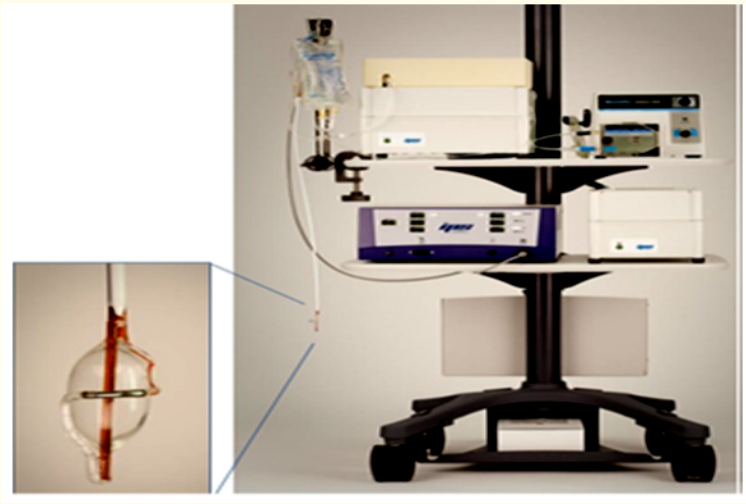

Figure 12: *First generation targeted lung denervation system. Dual cooled RF catheter and console.*

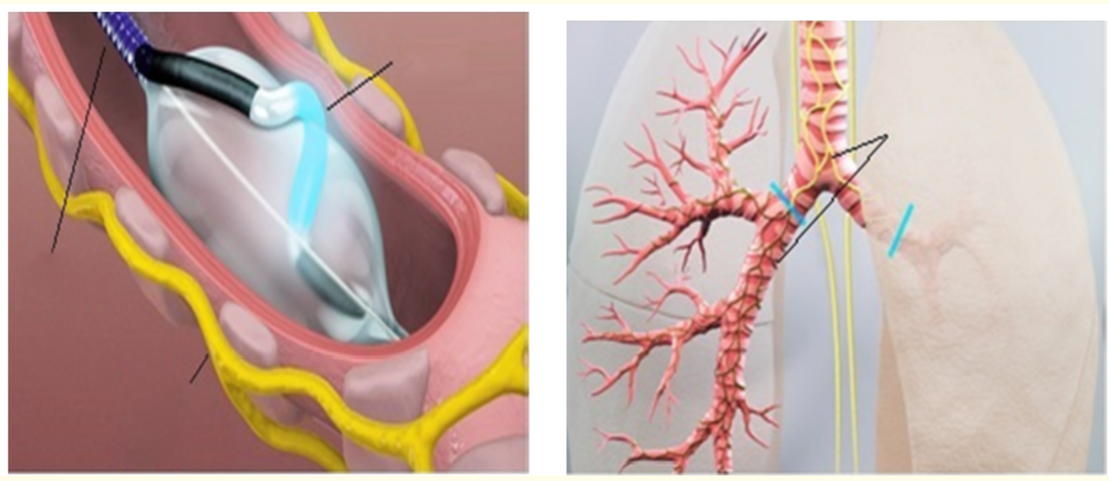

Figure 13: *Representative ablation procedure. (Left) Catheter is rotationally repositioned to achieve complete circumferential treatment. (Right) Blue lines designate the area of circumferential ablation in main bronchi.*

The first-in-human study was conduted by Slebos., *et al* [7]. This approach is shown to be feasible and safe. Safety defined as freedom from documented and sustained worsening of COPD directly attributable to the investigational device or procedure to 365 days post-TLD therapy, was achieved in 100%. No device-related adverse events were reported. Complications reported in one study over 1 year follow up of only 15 patients included: COPD exacerbations 13%, urinary retention 7%, and one worsening of an underlying arrhythmia 7% [41]. In Slebos study [7], Gastroparesis, bronchial stenosis, bronchial ulceration, COPD exacerbation and bronchial perforation had been reported. Due to low number of patients the incidence rate of complications need to be augmented by more studies with large number of patients.

(B) Bronchoscopic treatment of chronic bronchitis (Bronchial Rheoplasty)

Chronic bronchitis patients may benefit from ablation of mucus-producing airway cells. Bronchial Rheoplasty is a new procedure in which Pulsed Electric Fields are delivered to the airways via an endobronchial catheter. The First-in-Human study is an ongoing, multicenter study evaluating the safety and clinical effect of Bronchial Rheoplasty in patients with chronic bronchitis. Bronchial Rheoplasty is performed in two treatments, the first to treat the right lung airways and the second, one month later, to treat the left lung airways. A third bronchoscopy approximately three months after the second treatment is performed for sample collection only. Endobronchial cryobiopsies were obtained before treatment and at follow up and evaluated by an independent blinded core lab (Figure 14). Changes in symptoms, quality of life and pulmonary function were assessed. Early results demonstrate safety and feasibility of Bronchial Rheoplasty in chronic bronchitis patients. Further studies are required to confirm these results [8].

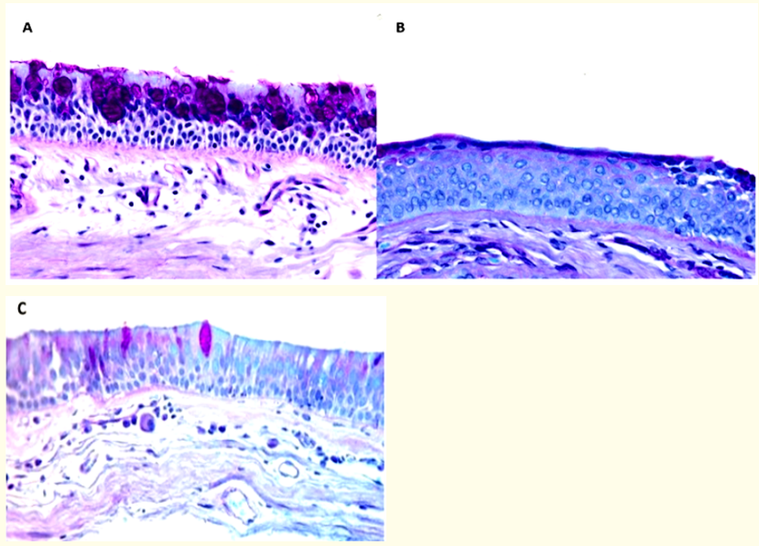

Figure 14: *Endobronchial histology from a patient treated with Bronchial Rheoplasty. A: Immediately before therapy significant goblet cell hyperplasia can be seen. B: At 30 days post treatment, the epithelium demonstrates squamous meraptasta, indicating a regenerative process. C: At 120 days after the initial treatment, there is complete regeneration of pseudostratified columnar epithelium with a resolution of goblet cell hyperplasia.*

Conclusion

Bronchoscopic lung volume reduction offers new treatment options for advanced emphysema patients. Several bronchoscopic techniques had been studied and proved to be feasible and safe. Good patient selection for each technique is crucial for optimizing the results. The evolving bronchoscopic treatment for chronic bronchitis has early promising results however further studies are required to confirm the safety and efficacy in a large group of patients.

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