

The bronchoscopic interventions for chronic obstructive pulmonary disease according to different phenotypes

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Abstract: Bronchoscopic interventions are valuable adjuncts to the pharmacologic therapy for chronic obstructive pulmonary disease (COPD). But different phenotypes of COPD patients showed different clinical responses to the same or similar therapy. The optimal selection of bronchoscopic interventions for COPD patients also needs to be based on the phenotypes. According to the different phenotypes, novel interventional pulmonology techniques which were used for COPD treatments in daily clinical practice or clinical trials have been described extensively throughout our current review.

Keywords: Chronic obstructive pulmonary disease (COPD); phenotype; emphysema; chronic bronchitis; bronchoscopic lung volume reduction (BLVR); targeted lung denervation (TLD)

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent lung diseases in the world with high social burden (1). Pharmacological treatment options are limited and most only improve symptoms and airflow limitation without mortality benefit. The different phenotypes of COPD, for example chronic bronchitis phenotype, emphysema phenotype, have different characteristics which influence clinical response to medical treatment (2), so the global initiative for chronic obstructive pulmonary disease (GOLD) recommends an individualized therapy for COPD patients. In the past fourteen years, clinical trials of bronchoscopic interventions for the treatment of COPD have been developed greatly, and some techniques, such as bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBVs) or endobronchial coils (3-6), shown better efficacy and potential mortality benefit and were recommended by

GOLD in 2017 (2). Those techniques are valuable adjuncts to the pharmacologic therapy for COPD. But, how to select an individual and precise treatment for different phenotype of COPD is the key point in BLVR. In this review we will discuss the concepts and key points for each of these techniques and their indications for emphysema phenotype and chronic bronchitis phenotype of COPD.

BLVR for emphysema phenotype of COPD

The clinical presentations of emphysema phenotype of COPD are quite different from the ones of bronchitis phenotype. Hyperinflation and worse lung compliance are the main clinical manifestations of emphysema phenotype. COPD patients with predominant emphysema showed poor clinical response to long acting beta agonist (7). Based on the result of the National Emphysema Treatment Trial (NETT) study which showed surgical lung volume reduction was beneficial to the COPD patients with both

predominantly upper-lobe emphysema and low base-line exercise capacity (8), the attempt of BLVR was introduced into the therapy for severe COPD with emphysema gradually. No standard indications of BLVR exist now, an expert statement suggested that the potential candidates for BLVR were COPD patients with severe emphysema who were ex-smoker, and suffering from severe air flow restriction, hyperinflation, and low base-line exercise capacity [forced expiratory volume in the first second (FEV_1) $<50\%$ and residual volume (RV) $>175\%$, RV/total lung capacity (TLC) >0.58 , 6MWT 150–400 m], despite receiving the best medical treatments and having completed pulmonary rehabilitation and/or participating in a structured physical therapy program (9). BLVR can reduce the lung volume and hyperinflation, and improve the lung, chest wall and diaphragm mechanics. The key point of BLVR is realizing target lung volume reduction which is the fundamental of improvements in pulmonary function, exercise tolerance and health-related quality of life. But different techniques have different mechanisms to achieve lung volume reduction. So the best candidates for different techniques may be different. We briefly divided the techniques into two groups, blocking therapy and sclerosing therapy.

The blocking therapy of BLVR

The blocking therapy includes EBVs and endobronchial coils. EBV has a single direction valve which permits the air flow out from the target lung and prevents re-entry. It collapses the target lobe by blocking the target bronchus, but the existence of collateral ventilation (CV) influences the efficacy of BLVR with EBVs and leads to treatment failure (3,10). So pre-operative evaluation of CV is critical. Integrity of lobular fissure with high resolution computed tomography (HRCT) or detection CV with Chartis system is useful, with similar efficacy to predict the CV and target lung volume reduction (74% *vs.* 77%) (11). They are complementary (12), but when low flow phenotype of Chartis reading exists, the judgment of CV is challenged yet combining Chartis reading and HRCT analysis of fissure integrity (13,14). Once the CV is negative, the COPD patients with emphysema, regardless of whether heterogeneous or homogeneous, may get benefit from the BLVR with EBVs (15,16). During the procedure, we should select the right size EBV, and implant it into the right position (the proper depth of implantation of EBV and keeping coaxial with bronchial lumen) to accomplish

the completed occlusion of target bronchus. Previous randomized control trials such as VENT study, STELVIO study, BeLieVeR-HiFi study and EURO VENT study revealed that BLVR with EBVs could improve pulmonary function, quality of life, exercise tolerance in severe emphysema phenotype of COPD (3,4,15,16). Greater benefit was shown in the patients with heterogeneous emphysema than that of patients with homogeneous one (4). Although some studies showed that the patients with homogeneous emphysema whose CV was negative also could get significant benefit, the evidence was limited (16,17). Based on the studies, GOLD recommended the use of EBV in patients with severe emphysema whose CV was negative, with level of evidence B. More studies, such as LIVE study (18), are clearly indicated to evaluate the long term efficacy and safety of BLVR with EBVs, especially the impact on mortality rate. The common complications include pneumothorax, acute exacerbation of COPD, EBV migration and granulomatosis. The incidence of pneumothorax varies from 4.2% to 25.6% (3,17,19,20). Higher incidence of pneumothorax was observed in patients with target lung reduction, however, patients who complicated with pneumothorax could benefit more from BLVR with EBVs (21). Modifying post-operative medical care including strict 48 hours bed rest and cough suppression could reduce pneumothorax incidence in patients with upper lobe as the target lobe, but it could not reduce the pneumothorax incidence in patients with lower lobe as treated lobe (22).

For the COPD patients whose CV is positive, an ‘indirect blocking’ therapy, endobronchial coils, can be an alternative. Endobronchial coils are shape-retaining nitinol devices implanted into the sub-segmental bronchus by a straight deliver sheath, when the coil recover its original shape, it makes the target bronchus twisted and ‘completely blocked’ to achieve parenchymal compression and atelectasis. So the lung volume reduction led by endobronchial coils is not influenced by the existence of CV. Three randomized trials [RESET study (23), REVOLENS study (6) and RENEW study (5)] showed that endobronchial coils implantation could achieve lung volume reduction and improve the quality of life, pulmonary function, and exercise capacity with statistically and clinically significance in patients with severe emphysema phenotype of COPD (5,6,23). RESET study was the first study to point out that endobronchial coils were beneficial to patients with homogeneous emphysema. A meta-analysis enrolled four European clinical trials indicated that there were no differences in efficacy and safety of endobronchial

coils between heterogeneous and homogeneous emphysema patients. A high baseline RV was the single independent predictor of the success of treatment (24). So the endobronchial coils were recommended to be used in severe COPD patients with hyperinflation regardless of the existence of CV or the heterogeneity of emphysema. The common complications include acute exacerbation of COPD, pneumonia, pneumothorax and thoracic pain (24). When these complications happened, the coils would be difficult to be removed, even there were some cases with reversible implantation of endobronchial coils (25). This is quite different from EBVs which is easily to be removed by forceps. Some nonrandomized trials showed the long term effect of BLVR with endobronchial coils, but the long-term randomized trials is still needed to answer the long-term safety and efficacy, especially the impact on mortality rate (26,27).

The sclerosing therapy of BLVR

The sclerosing therapy of BLVR includes BLVR with vapor, sclerosants, autologous blood and fibrin glue, etc. BLVR with vapor, so called bronchoscopic thermal vapour ablation (BTVA), is a technique through which delivering heated steam to the target segmental or sub-segmental lobe. Then thermal energy from the heated steam will lead the localized non-infectious inflammation in the target lobe, which causes fibrosis and atelectasis to achieve lung volume reduction. The dose of vapor energy is calculated at segmental level according to the tissue-to-air ratio on density measurement of HRCT. The most important study of BTVA is STEP-UP study. The 6- and 12-month follow-up results found that there were significant improvements in FEV₁ and quality of life measured by the St Georges Respiratory Questionnaire (SGRQ) in the patients who received BTVA therapy (28,29). The patients with more respiratory adverse events associated with the localized inflammatory response in the first 30 days after BTVA experience greater efficacy (30). The existence of CV did not influence the efficacy of BTVA (31). So the BTVA could be a potential therapy for patients with heterogeneous emphysema. But the long-term efficacy should be evaluated carefully in the future because the previous study has showed that the improvements in pulmonary function and six minutes walking distance at 6th month but declined at 12th month.

Biological lung volume reduction (BioLVR) is a novel type of BLVR, which delivers polymerizing sealant into the bronchioles, and block off the distal airspace in the patients with severe emphysema. The mechanisms of BioLVR

involve the resorption of atelectasis from airway occlusion, subsequent airspace inflammation, and the repair with scar formation. The only randomized clinical trial of BioLVR showed that the treatment with AeriSeal System (ELS; Pulmonx, Neuchatel, Switzerland) could significantly and clinically improve the lung function, dyspnea score, and quality of life when comparing to the control group at 3rd and 6th month (32). Two previous pilot studies also provided valuable results for the clinical practice of BioLVR. BioLVR could improve the pulmonary function, exercise capacity and quality of life in patients with severe upper lobe predominant emphysema regardless of the existence of CV (33). The common complication of BioLVR with AeriSeal System is treatment associated acute inflammatory response including fever, dyspnea, cough, chest pain and/or elevated inflammatory markers (34). So a 7-day steroid tapering and prophylactic antibiotic therapy are recommended before the initiation of BioLVR.

A pilot open label study also evaluated the efficacy and safety of BLVR using autologous blood and fibrin glue, and demonstrated that it was an effective and safe therapy for advanced emphysema with better cost effectiveness at 12 weeks post-procedure (35). But the small sample size and lack of short-term follow-up reduced the power of the study. Further studies are needed to evaluate the long-term efficacy and safety.

Although accumulated data showed that bronchoscopic interventions were potential alternatives to LVRS. But some questions about the techniques mentioned above, such as how to prevent and reduce the treatment associated inflammatory response, how to predict the clinical response, and how to maintain the long-term efficacy, are needed to be clarified.

BLVR for chronic bronchitis phenotype of COPD

Acetylcholine is the primary parasympathetic neurotransmitter in the airways which binds with M3 receptors and leads to bronchoconstriction (36). Cholinergic tone in COPD patients is increased and lead to the reversible airflow obstruction and promotion of airway inflammation and remodeling (36). It is one of main mechanisms of airflow limitation in chronic bronchitis phenotype of COPD patients. LAMA is effective and the first line bronchodilator for patients with moderate to severe COPD and also shown anti-inflammatory effects (2). Disruption of parasympathetic pulmonary nerves may improve lung function and the symptoms, and decrease the airway inflammation of patients

with COPD. Targeted lung denervation (TLD) is a novel technique which based on ablation of parasympathetic pulmonary nerves surrounding the main bronchi. It is a potential therapy for chronic bronchitis phenotype of COPD. A pilot study showed that TLD was feasible, safe, and well tolerated in patients with COPD ($FEV_1/FVC < 0.70$; FEV_1 30–60% predicted) (37), and TLD could inhibit the airway inflammation not only by reducing the levels of neutrophils and protein expression of CXCL8 and CCL4 in the bronchial wash, but also through reducing the gene expression of CXCL8, IL-6, TGF- β and MUC5AC in the bronchial brush (38). So far, three clinical trials are ongoing to evaluate the safety and efficacy of TLD. We believe the question that can TLD be a novel surrogate to LAMA in treatment of patients of chronic bronchitis phenotype will be solved.

Conclusions

Bronchoscopic interventions bring novel insights into the treatment of severe COPD with different phenotypes. Some bronchoscopic interventions have shown efficacy in severe COPD patients who were already receiving the maximum available treatment, and were recommended by the guideline of treatment of COPD, and others need more clinical trials to confirm its long-term effect and safety. The optimal standards of patient selection for different bronchoscopic interventions are also needed to be clarified in the future.

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Footnote

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References

- Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347-65.
- the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. 2017. Available online: <http://goldcopd.org>
- Sciruba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med* 2010;363:1233-44.
- Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. *N Engl J Med* 2015;373:2325-35.
- Sciruba FC, Criner GJ, Strange C, et al. Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema: The RENEW Randomized Clinical Trial. *JAMA* 2016;315:2178-89.
- Deslee G, Mal H, Dutau H, et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. *JAMA* 2016;315:175-84.
- Lee JH, Lee YK, Kim EK, et al. Responses to inhaled long-acting beta-agonist and corticosteroid according to COPD subtype. *Respir Med* 2010;104:542-9.
- Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059-73.
- Herth FJ, Slebos DJ, Rabe KF, et al. Endoscopic Lung Volume Reduction: An Expert Panel Recommendation. *Respiration* 2016;91:241-50.
- Iftikhar IH, McGuire FR, Musani AI. Predictors of efficacy for endobronchial valves in bronchoscopic lung volume reduction: A meta-analysis. *Chron Respir Dis* 2014;11:237-45.
- Gompelmann D, Eberhardt R, Slebos DJ, et al. Diagnostic performance comparison of the Chartis System and high-resolution computerized tomography fissure analysis for planning endoscopic lung volume reduction. *Respirology* 2014;19:524-30.
- Koster TD, van Rikxoort EM, Huebner RH, et al. Predicting Lung Volume Reduction after Endobronchial Valve Therapy Is Maximized Using a Combination of Diagnostic Tools. *Respiration* 2016;92:150-7.
- Shah PL, Herth FJ. Dynamic expiratory airway collapse and evaluation of collateral ventilation with Chartis. *Thorax* 2014;69:290-1.
- Yin Y, Hou G, Herth FJ, et al. Significant lung volume reduction with endobronchial valves in a patient despite the presence of microcollaterals masked by low-flow Chartis phenotype. *Int J Chron Obstruct Pulmon Dis* 2016;11:2913-7.
- Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients

- with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. *Lancet* 2015;386:1066-73.
16. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. *Eur Respir J* 2012;39:1334-42.
 17. Valipour A, Slebos DJ, Herth F, et al. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. *Am J Respir Crit Care Med* 2016;194:1073-82.
 18. Skowasch D, Fertl A, Schwick B, et al. A Long-Term Follow-Up Investigation of Endobronchial Valves in Emphysema (the LIVE Study): Study Protocol and Six-Month Interim Analysis Results of a Prospective Five-Year Observational Study. *Respiration* 2016;92:118-26.
 19. Trudzinski FC, Hoink AJ, Leppert D, et al. Endoscopic Lung Volume Reduction Using Endobronchial Valves in Patients with Severe Emphysema and Very Low FEV1. *Respiration* 2016;92:258-65.
 20. Choi M, Lee WS, Lee M, et al. Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2015;10:703-10.
 21. Gompelmann D, Herth FJ, Slebos DJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. *Respiration* 2014;87:485-91.
 22. Herzog D, Poellinger A, Doellinger F, et al. Modifying Post-Operative Medical Care after EBV Implant May Reduce Pneumothorax Incidence. *PLoS One* 2015;10:e0128097.
 23. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. *Lancet Respir Med* 2013;1:233-40.
 24. Slebos DJ, Hartman JE, Klooster K, et al. Bronchoscopic Coil Treatment for Patients with Severe Emphysema: A Meta-Analysis. *Respiration* 2015;90:136-45.
 25. Dutau H, Bourru D, Guinde J, et al. Successful Late Removal of Endobronchial Coils. *Chest* 2016;150:e143-5.
 26. Zoumot Z, Kemp SV, Singh S, et al. Endobronchial coils for severe emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial. *PLoS One* 2015;10:e0122656.
 27. Hartman JE, Klooster K, Gortzak K, et al. Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema. *Respirology* 2015;20:319-26.
 28. Gompelmann D, Heussel CP, Eberhardt R, et al. Efficacy of bronchoscopic thermal vapor ablation and lobar fissure completeness in patients with heterogeneous emphysema. *Respiration* 2012;83:400-6.
 29. Herth FJ, Ernst A, Baker KM, et al. Characterization of outcomes 1 year after endoscopic thermal vapor ablation for patients with heterogeneous emphysema. *Int J Chron Obstruct Pulmon Dis* 2012;7:397-405.
 30. Gompelmann D, Eberhardt R, Ernst A, et al. The localized inflammatory response to bronchoscopic thermal vapor ablation. *Respiration* 2013;86:324-31.
 31. Gompelmann D, Eberhardt R, Schuhmann M, et al. Lung Volume Reduction with Vapor Ablation in the Presence of Incomplete Fissures: 12-Month Results from the STEP-UP Randomized Controlled Study. *Respiration* 2016;92:397-403.
 32. Come CE, Kramer MR, Dransfield MT, et al. A randomised trial of lung sealant versus medical therapy for advanced emphysema. *Eur Respir J* 2015;46:651-62.
 33. Magnussen H, Kramer MR, Kirsten AM, et al. Effect of fissure integrity on lung volume reduction using a polymer sealant in advanced emphysema. *Thorax* 2012;67:302-8.
 34. Herth FJ, Gompelmann D, Stanzel F, et al. Treatment of advanced emphysema with emphysematous lung sealant (AeriSeal(R)). *Respiration* 2011;82:36-45.
 35. Bakeer M, Abdelgawad TT, El-Metwaly R, et al. Low cost biological lung volume reduction therapy for advanced emphysema. *Int J Chron Obstruct Pulmon Dis* 2016;11:1793-800.
 36. Gross NJ, Skorodin MS. Role of the parasympathetic system in airway obstruction due to emphysema. *N Engl J Med* 1984;311:421-5.
 37. Slebos DJ, Klooster K, Koegelenberg CF, et al. Targeted lung denervation for moderate to severe COPD: a pilot study. *Thorax* 2015;70:411-9.
 38. Kistemaker LE, Slebos DJ, Meurs H, et al. Anti-inflammatory effects of targeted lung denervation in patients with COPD. *Eur Respir J* 2015;46:1489-92.

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