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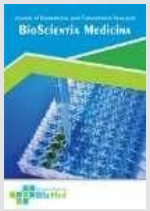

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Bronchoscopic Lung Volume Reduction as Therapy in Chronic Obstructive Pulmonary Disease (COPD) Patients with Emphysema

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A B S T R A C T

BLVR is a combination of non-surgical techniques for lung volume reduction performed via bronchoscopy as an alternative to LVRS in emphysema patients. The techniques most often used in BLVR are bronchial valves (EBV/IBV), coils (lung coil), and thermal vapor (BTVA), while the BioLVR and ABS techniques have begun to be abandoned. BLVR is generally beneficial in improving lung function, exercise capacity, and quality of life in patients with emphysema. There is a need to monitor post-procedure side effects and long-term follow-up to assess the effectiveness of the procedure and reduce complications.

1. Introduction

Chronic obstructive pulmonary disease (COPD) has a prevalence of 10%, with over 300 million people affected worldwide, and is the fourth leading cause of death in the United States.[1] Emphysema is a type of COPD that is characterized by irreversible and progressive destruction of the alveolar structure in line with the loss of lung recoil elasticity. COPD progression can continue despite medical therapy and pulmonary rehabilitation, requiring the exploration of alternative therapeutic interventions.[2] Bronchoscopic lung volume reduction (BLVR) is emerging as a promising therapy in appropriately selected patients.

Bronchoscopic lung volume reduction consists of a combination of non-surgical techniques for lung volume reduction that are performed via bronchoscopy and allow the operator to access the trachea and lower airways through the nose or mouth, thereby eliminating the need for surgical procedures. A meta-analysis study in 2015 found a significant increase in forced expiratory volume in the first second (VEP1) of up to 200 ml and a decrease in volume residue (VR) of up to 680 ml on pulmonary function tests. An increase in exercise capacity as measured by the 6-minute walk test up to 91 m was also found in patients after the BLVR procedure. A significant improvement in

quality of life after undergoing BLVR was also seen in the results of the examination using the St George's Respiratory Questionnaire (SGRQ) or modified Medical Research Council (mMRC).[3]

There are various techniques that can be used in the BLVR procedure, but the one most frequently used today is the endobronchial valve/intrabronchial valve (EBV/IBV), lung volume reduction coil (LVRC), and bronchoscopic thermal vapor ablation (BTVA). These three techniques are considered the most useful with minimal side effects.[3]

Bronchoscopic lung volume reduction

Bronchoscopic lung volume reduction (BLVR) is a minimally invasive procedure that aims to improve lung function and quality of life in patients with emphysema. Emphysema is a progressive lung disease characterized by damage to alveolar tissue, which causes decreased lung function and difficulty breathing. Bronchoscopic lung volume reduction is considered as an alternative to lung volume reduction surgery (LVRS) and has shown promising results in patients with chronic emphysema.[4-7] BLVR consists of a combination of non-surgical techniques to reduce lung volume performed via bronchoscopy. The operator needs to identify the part of the lung that has emphysema via computerized tomography (CT), ventilation/perfusion scintigraphy, or magnetic resonance imaging (MRI). Then, after BLVR, finding target areas can be done through several different techniques.[3]

Bronchial valves

The bronchial valves used in BLVR are generally divided into endobronchial valves (EBV) and intrabronchial valves (IBV). The difference between these two types of valves can be seen from the shape of the valve itself; EBV has a shape like a duck color (for example, Zephyr), while IBV is shaped like an umbrella (for example, spiration). The mechanism of action of EBV and IBV is by forming a one-way valve that aims to close and form atelectasis in the most damaged lung lobe so that it does not receive air during inspiration but still allows secretions and air to escape from the blocked part of the lung. This technique targets specific areas of the lung that are emphysema, so this technique is suitable for heterogeneous emphysema.[3,8]

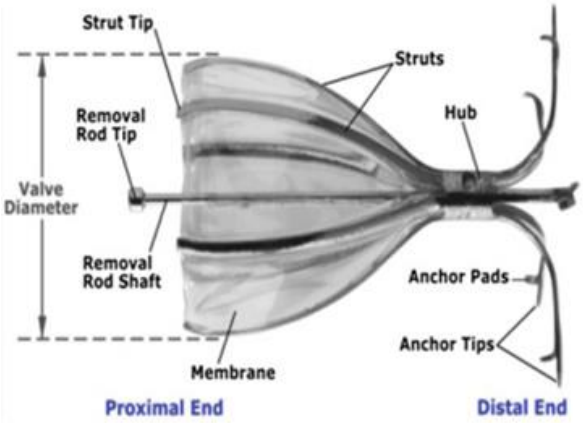

Figure 1. Intrabronchial valve (spiration).

The size of the bronchial valve is selected according to the size of the bronchial lumen selected for the procedure. A catheter equipped with a balloon is inflated using a syringe at the location of the bronchus where the valve will be installed, and then the amount of fluid that enters through the syringe is converted using a special table to determine the valve size to be used. The valve is placed in the bronchoscope while it is compressed; then, once the target lumen is found, a special catheter is used to place the valve. The buffer is covered by a membrane that acts as an airflow barrier and an anchor that keeps the valve in place. The procedure can be repeated for both types of valves to restore position and function if the valve shifts from the desired position. The selection of patients for whom this procedure will be performed is very important because the heterogeneity of the disease and the presence of collateral ventilation can influence the response to therapy.[2,9]

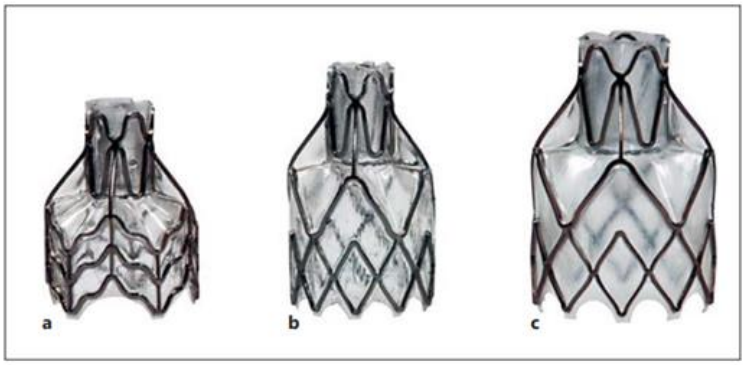

Figure 2. Endobronchial valve (zephyr) with diameters of 4.0 mm, 5.5 mm, and 8.5 mm.

This technique uses a lung coil/coil made from nitinol, which is designed to be anchored in the airway, thereby reducing the volume of the lung that is experiencing abnormalities, especially in patients with heterogeneous emphysema. RePneu coils measuring 100 mm, 125 mm, or 150 mm will then be inserted using a catheter via a guide wire (mandrain). The coil remains straight while it is in the bronchoscope. Then, after being placed into the target lumen, it will return to its original coil shape. The installed coil will shorten the airway and pull in the lung tissue that is experiencing emphysema, thereby providing space for healthy lung tissue to expand during inspiration.[11]

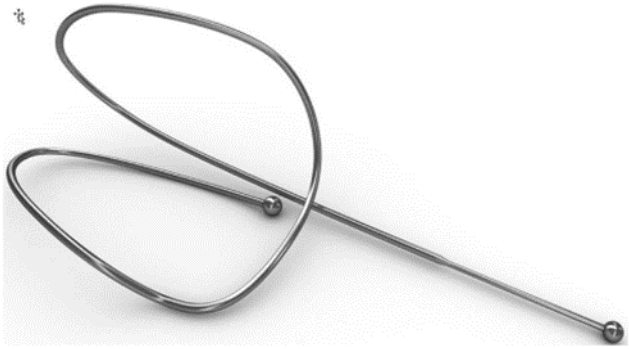

Figure 3. The lung coil (RePneu) is made from nitinol.

Consideration for treatment using coils relies on CT assessment to rule out contraindications and to determine the extent of lung parenchymal damage to improve the effectiveness of therapy. For each procedure, 8 – 14 coils (average 10 coils) can be placed in the bronchial subsegment of the lobe that is experiencing abnormalities. Coil installation can still be done in patients with collateral ventilation because the mechanism of action is completely different from bronchial valves, namely by mechanically restoring the elasticity of the lungs.[8,12]

Bronchoscopic thermal vapor ablation (BTVA)

Bronchoscopic thermal vapor ablation (BTVA) aims to induce lung tissue shrinkage through thermal injury using water vapor. The local inflammatory reaction will result in fibrosis and scar tissue formation after 8-12 weeks and a reduction in volume in the lung lobe undergoing the procedure. This procedure is irreversible and is chosen in patients with upper lobe emphysema and no collateral ventilation.[8,13]

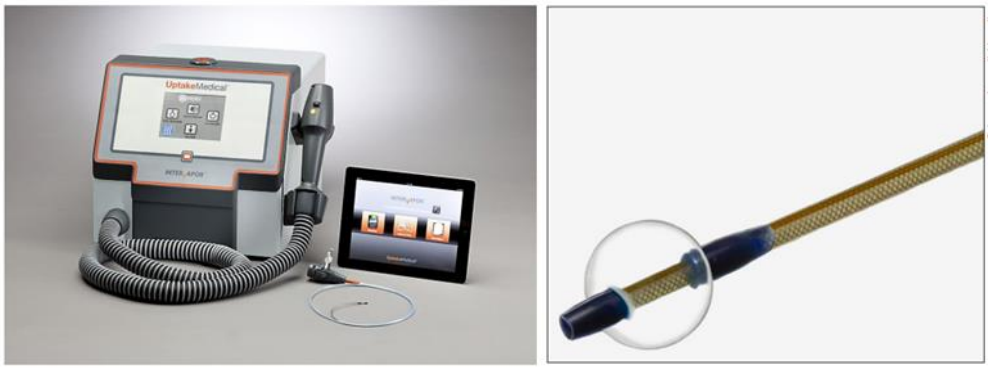

Figure 4. BTVA (intervapor generator) is a device with a catheter equipped with a balloon.

A bronchoscope equipped with an occlusion balloon is directed at a predetermined area of emphysema using CT. The balloon is inflated, and the steam at a temperature of approximately 75°C is delivered to the lung segment that has emphysema. The average steam dose is 10 cal/g of alveolar tissue. This vapor will later cause an inflammatory response that causes fibrosis and collapse of the distal airways.[11]

BioLVR

BioLVR or polymer LVR is a method of bronchoscopic instillation of hydrogel into the target lobe to trigger atelectasis in that lobe. AeriSeal (Aeris Therapeutics, Inc., Woburn, MA, USA) is a foam-shaped liquid medium that is used on bronchioles and alveoli with a volume of 10 mL (low dose) or 20 mL (high dose) for each part. This polymer foam installation is an irreversible BLVR procedure. Bronchoscopically applied polymer resin causes fibrosis in the targeted lung parenchyma. The inflammatory reaction then functions to shrink the tissue in the target area and reduce the volume. The first study involving 14 patients published in 2011 reported that positive therapeutic effects were clearly visible in patients undergoing BioLVR, but complications were also frequently encountered, especially inflammatory processes induced by BioLVR. The ASPIRE study conducted in 2014 compared BioLVR with medical therapy, and BioLVR has since been abandoned due to high levels of side effects and complications requiring hospitalization. Until now, the BLVR technique using BioLVR has not been recommended.[3,8]

Airway bypass stent (ABS)

Airway bypass stent (ABS) is a bronchoscopic lung volume reduction procedure designed for the treatment of severe homogeneous emphysema. This technique aims to create a channel from the airway

wall to the part of the lung experiencing emphysema to remove air trapped in that area. A low-dose drug (paclitaxel)-coated stent is inserted into each created channel. This stent is made of stainless steel and silicone and contains paclitaxel, which is intended to inhibit the fibrotic response so that bypass occlusion can be avoided.[8]

The study by Choong et al. in 2009 reported that ABS improved lung function parameters and reduced respiratory disorders, but in 2011, the "EASE" study involving 315 patients with severe homogeneous emphysema reported no statistically significant differences between patients who underwent ABS and patients who received only therapy. medicamentosa. ABS is reported to be effective in the short term, but its effectiveness decreases over time, which is thought to be due to factors involving mucus plugging and granuloma formation around the stent. Further research is needed to optimize treatment methods. Currently, this method is not one of the frequently used BLVR treatments due to the low long-term efficacy and high risk of pneumothorax complications.[3,8]

Indications and contraindications

The indications for BLVR do not differ much for each technique. Indications for BLVR include emphysema diagnosed via chest CT scan, post-bronchodilator FEV1 <15%-50% predicted, VR >175%, total lung capacity >100%, 6-minute walk test >150 m, no pulmonary hypertension, $PaCO_2$ < 50-55 mmHg, and quit smoking >2 months previously. Table 1 shows the general indications for BLVR.[15]

Table 1. Indications for BLVR based on the technique used.

Method	VEP1 %pred	VR %pred	KTP %pred	$PaCO_2$ mmHg	TJ6MM	Stop smoking
Valve	15-50	>175	>100	<60	100-500	>6 months
Coil	15-45	>175	>100	<55	150-450	>6 months
BTVA	20-45	>175	>100	<55	>140	>4 months

Spirometry and hyperinflation

There is no absolute cut-off in spirometry when considering patients for BLVR; however, in clinical practice and clinical trials, the majority of patients have a post-bronchodilator VEP1 of 15% - 50% prediction. It is also important to select patients who have hyperinflated lungs because the primary goal of BLVR is to reduce lung hyperinflation. Consistent with previous trials and expert recommendations, patients had to show evidence of hyperinflation measured by total lung capacity >100% and VR >175%.[15,16]

Exercise capacity

Patients must have maintained exercise capacity at a certain level to tolerate the procedure and potential complications. Patients with a 6-minute walk test between 100 and 500 m may be considered for a BLVR procedure. Patients with a 6-minute walk test result of less than 200 meters are recommended to undergo pulmonary rehabilitation first and then undergo another 6-minute walk test assessment.[10]

Emphysema morphology

A chest CT scan is needed to evaluate the degree and distribution of emphysema. This examination can help determine which lobe has more damage to take action. It should be noted in determining the location of the procedure whether there are bullae in the lobe (which may indicate the need to be alert for pneumothorax after the procedure), nodules (which require further assessment and/or follow-up), infiltrates or cavities (which may indicate an infection that must be treated first). previously), or other conditions that require consideration not to take action (such as severe bronchiectasis, extensive fibrosis, etc.).[10,17]

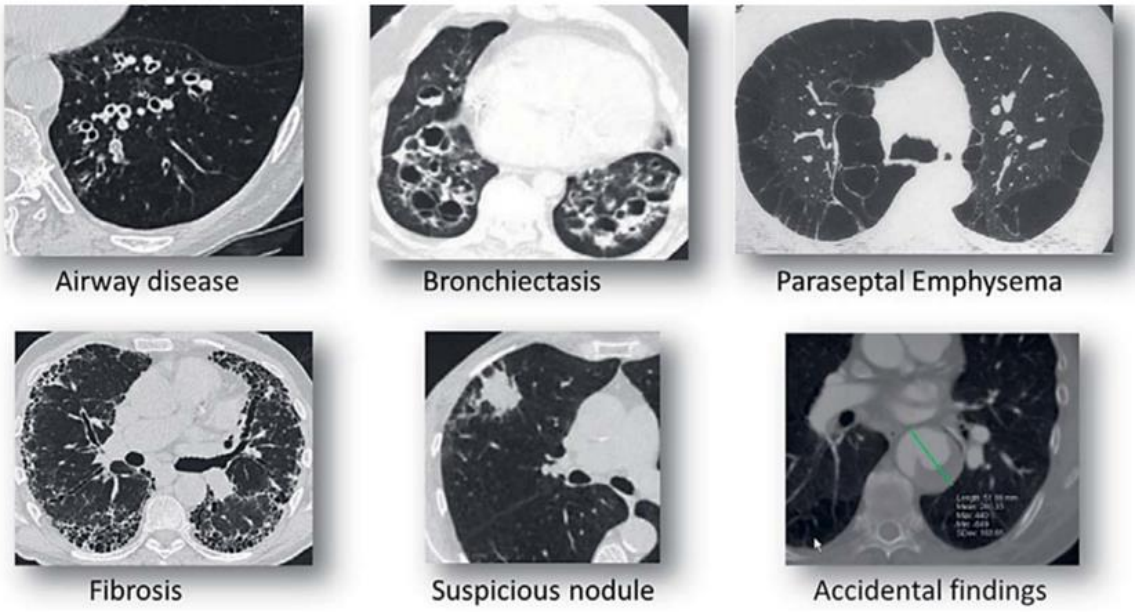

Figure 5. Chest CT scan images that are not recommended for BLVR.

Collateral ventilation

Especially for BLVR that uses a bronchial valve, the presence of collateral ventilation between the target lobe and the ipsilateral lobe is important for the success of the procedure. The Chartis system is a diagnostic tool that can be used to identify the presence of collateral ventilation in the target lobe. The assessment is carried out by inserting a special flexible bronchoscope equipped with a balloon and sensors to detect airflow. The balloon is inflated at the ostium of the lobe, which will be inspected until it covers the entire lumen; then, the sensor will detect a decrease in airflow during expiration. If there is collateral ventilation, the airflow during expiration will remain constant due to leakage from adjacent lobes.[13,18]

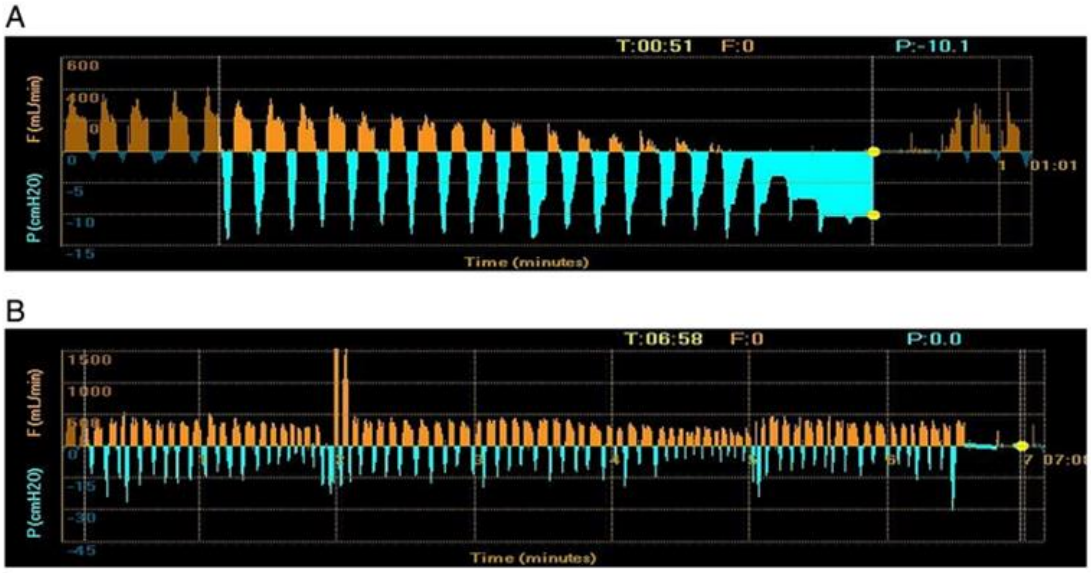

Figure 6. The results of examination with the Chartiz system show (A) there is no inter-lobe collateral ventilation and (B) there is inter-lobe collateral ventilation.

Visual assessment of lobar fissure integrity using HRCT is also a method that is often used to assess the presence of collateral ventilation but is not recommended because it is subjective and has high interoperator variability. Recent research supports the use of HRCT for screening patients undergoing BLVR with bronchial valves. Patients with fissure integrity <80% based on HRCT assessment are not considered for EBV treatment, while patients with fissure integrity between 80 and 95% require Chartis examination to confirm the absence of collateral ventilation. Patients with fissure integrity >95% can immediately undergo bronchial valve installation with Chartis only as a consideration.[16,18]

Procedure complications

BLVR procedure with bronchial valve installation is associated with several risks of complications such as COPD exacerbation (9.3%-64.0%), pneumonia (11.7%), pneumothorax (4.2%-29.2%), migration, and replacement. valve (1.5%-20.0%). The presence of collateral ventilation between lobes in patients also reduces the effectiveness of bronchial valve installation. Complications in BLVR using coils are reported to be relatively higher compared to bronchial valves, including exacerbation of COPD (10.8%-87.0%), pneumonia (0%-46.0%), and pneumothorax (5.6%-31, 6%). Another complication that is more frequently encountered with coil use is persistent pleuritic chest pain that requires coil extraction.[8,19]

BTVA actions most often cause side effects immediately after the action that show signs of excessive inflammation marked by respiratory symptoms, such as shortness of breath, cough, fever, and mild hemoptysis. A heavy inflammatory response is related to more frequent treatment figures but also correlates with a better benefit in the follow-up 6th month. Other common complications are pneumonia (18%-23%) and exacerbation of COPD (9%-24%), so it is necessary to follow up strictly during hospitalization after the procedure. Simultaneous administration of prophylactic antibiotics and anti-inflammatories can be considered, but there are no definite guidelines regarding this.[20,21]

Benefits and limitations

Various studies have assessed the benefits of BLVR through several aspects, namely improving lung function (especially VEP1), tolerance to physical activity (assessed by the 6-minute walk test), and improving quality of life (via the SGRQ or MMRC questionnaire). The use of bronchial valves showed a significant increase in VEP1 with an average increase of 77.5 mL (34.5 mL - 140 mL) and 13.7% (4.3% - 20.7%) and a decrease in Residue Volume (VR) of 440 mL (200 mL – 680 mL). The 6-minute walk test also showed an increase of 40.8 m (9.3 m – 91.0 m). The BLVR procedure with bronchial valves is reversible. The valve can be removed or repositioned if a malfunction occurs. Collateral ventilation is the only important note that can reduce the effectiveness of this action.[19,22]

The use of coils in BLVR was also proven to increase VEP1 130 mL (90 mL - 200 mL) and 12.1% (7% - 14 %), decrease VR 420 ml (310 mL - 510 mL), and increase 47 m (14.6 -84.0 m) on a 6-minute walk test. Another study showed that after 6 months of treatment, there was a reduction in lung lobe volume by 48% and a significant improvement in lung function parameters and quality of life. There was a significant increase in FEV1 130 mL (63 mL - 198 mL) and 14.7% (7.8% - 21.5%), a decrease in VR (400 mL – 710 mL), and an increase in the 6-minute walk test (1, 5 m – 62.4 m) on follow up after 6 months. The reduction in lung volume by coils is mechanical and is not influenced by the presence or absence of collateral ventilation, so it can be used as an alternative if the use of a bronchial valve is not possible. The high number of complications, such as pneumothorax and discomfort (pleuritic chest pain, coughing up mild blood), are the disadvantages of this procedure.[19,23]

Table 2. Comparison of the advantages and disadvantages of the BLVR technique.

Benchmark	EBV/IBV	Coil	Thermal vapor
Reversibility	Reversible	Irreversible	Irreversible
Influence of collateral veins	Yes	No	No
Increased VEP1	34,5-140 mL	90-200 mL	64-141 mL
Decreased VR	200-680 mL	310-510 mL	108-406 mL
Increased TJ6M	9,3-91,0 m	14,6-84,0 m	18,3 m

There are far fewer publications regarding BTVAs compared to bronchial valves or coils. Research Herth et al. in 2016 reported the BTVA procedure with a steam dose of 10 cal/g in 44 patients, showing an increase in VEP1 of 101 mL (64 mL – 141 mL), a decrease in VR of 284 mL (108 mL-406 mL) and an increase of 18.3 m on the 6-minute walk test. These results are not much different from the bronchial valve or coil technique, but considering the high inflammatory response after this procedure makes BTVA less attractive than the other 2 procedures.[19,24]

2. Conclusion

BLVR is a combination of non-surgical techniques for lung volume reduction performed via bronchoscopy as an alternative to LVRS in emphysema patients. The techniques most often used in BLVR are bronchial valves (EBV/IBV), coils (lung coil), and thermal vapor (BTVA), while the BioLVR and ABS techniques have begun to be abandoned. BLVR is generally beneficial in improving lung function, exercise capacity, and quality of life in patients with emphysema. There is a need to monitor post-procedure side effects and long-term follow-up to assess the effectiveness of the procedure and reduce complications.

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