Medical Policy Manual Surgery, Policy No. 184

Bronchial Valves

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IMPORTANT REMINDER

DESCRIPTION

Bronchial (endobronchial, intrabronchial) valves are synthetic devices that are deployed with bronchoscopy into ventilatory airways of the lung for the purpose of controlling airflow.

MEDICAL POLICY CRITERIA

I. The use of a bronchial valve may be considered **medically necessary** for the treatment of *severe emphysema* when all of the following Criteria (A.- O.) are met:

A. The valve has been approved by the FDA (Zephyr® Endobronchial Valve System or Spiration® Valve System); and

B. Patient is age 40 years or older; and

C. Body mass index (BMI) less than 35kg/m^2; and

D. Patient has completed a pulmonary rehabilitation program prior to valve placement; and

E. The patient is not a cigarette smoker OR there is clinical documentation that the patient has been abstinent from cigarette smoking for at least four consecutive months prior to and throughout evaluation for the procedure; and

F. Little or no collateral ventilation as determined using the Chartis (Zephyr) or

SeleCT (Spiration) systems (see Policy Guidelines) is present; and

G. Total lung capacity (TLC) is greater than 100% predicted; and

H. Six-minute walking distance (6MWD) ≥100m and <500m; and

I. Patient has not had any of the following: prior lung transplant, lung volume reduction surgery (LVRS), ipsilateral bullectomy, or lobectomy; and

J. Residual volume (RV) is greater than or equal to 175% predicted; and

K. High resolution computed tomography (HRCT) obtained within 90 days of screening demonstrates all of the following (1.- 3.):

   1. *Absence* of large bullae encompassing greater than 30% of either lung; and
   2. Target lobe has greater than or equal to 40% emphysema destruction; and
   3. Greater than or equal to 10% disease severity difference (heterogenous emphysema) between the targeted lobe and the ipsilateral lobe; and

L. Post-bronchodilator forced expiratory volume (FEV1) is between 15% and 45% of predicted value; and

M. PaCO2 <60mmHg and PaO2 >45mm Hg on room air; and

N. Stable with less than 20 mg daily of prednisone (or equivalent); and

O. Patient has *no record of any of the following contraindications* as documented by an echocardiogram, right heart catheterization, and/or electrocardiogram completed within 90 days from screening:

   1. Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure greater than 45 mm Hg); and
   2. Left ventricular ejection fraction (LVEF) less than 45%; and
   3. Evidence or history of cor pulmonale; and
   4. Congestive heart failure; and
   5. Resting bradycardia (less than 50 beats/min).

II. Removal, replacement, or revision of a U.S. Food and Drug Administration (FDA) approved bronchial valve (Zephyr® Endobronchial Valve System or Spiration® Valve System) may be considered **medically necessary** once the valve has been placed for the treatment of emphysema.

III. The use of a bronchial valve is considered **investigational** for all other indications, including but not limited to the following:

A. For the treatment of emphysema when Criterion I. is not met; or

B. For the treatment of air leaks.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

The goal of bronchial valve treatment is to achieve a lobar volume reduction or atelectasis (collapse). In many patients, atelectasis cannot be achieved due to interlobar collateral ventilation (CV) generated through incomplete lobar fissures. There are several methods to assess the presence of CV, with endobronchial pulmonary assessment (e.g., the Chartis System) and CT-fissure analysis (e.g., SeleCT or StratX) being the most common.

CT-fissure analysis can be used to assess the completeness of the fissure. Typically, the analysis is done by experienced radiologists or pulmonologists. The target lobe and ipsilateral lobe must be separated with an intact fissure and an intact fissure is estimated visually to be ≥90% complete with no segmental vessels crossing from one lobe to the adjacent lobe after viewing the high-resolution CT in three dimensions (sagittal, axial, and coronal). Automated methods (SeleCT) to provide exact quantifications and support visual readings are recommended.

The Chartis system is used for bronchoscopic assessment of collateral ventilation and consists of a catheter with a balloon component at the distal tip. The Chartis system was originally validated in spontaneous breathing patients under conscious sedation, however the measurement has been performed under general anesthesia with positive pressure support or high frequency jet ventilation. The airway is blocked when the balloon is inflated and air from the targeted segment or lobe can flow only through the catheter. This air is directed to the Chartis console, which can assess both expiratory air flow, pressure, and resistance. Presence of collateral airflow is observed if expiratory airflow persists after occlusion of a lobe, and if there is no flow, this indicates no collateral airflow.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Medical records, including history and physical/chart notes related to documenting that all of the requirements in Criteria I. are met, including but not limited to:
    - results of high-resolution CT obtained within 90 days of screening documenting the sub-criteria in Criterion I. are met
    - results of echocardiogram, right heart catheterization, and/or electrocardiogram documenting sub-criteria in Criterion I. are met
    - the type of valve system to be used.

CROSS REFERENCES

None

BACKGROUND

Proper lung functioning is dependent upon a separation between the air-containing parts of the lung and the small vacuum-containing space around the lung called the pleural space. When air leaks into the pleural space, the lung is unable to inflate resulting in hypoventilation and hypoxemia; this condition is known as a pneumothorax. A pneumothorax can result from a variety of processes including trauma, high airway pressures induced during mechanical ventilation, lung surgery, and rupture of lung blebs or bullae, which may be congenital or a result of chronic obstructive pulmonary disease (COPD).

Bronchial valves are synthetic devices deployed with bronchoscopy into ventilatory airways of the lung to control airflow. They have been investigated for use in patients who have prolonged bronchopleural air leaks and as an alternative to lung volume reduction surgery in patients with hyperinflation from severe or advanced emphysema.

Emphysema, a form of COPD, is a progressive, debilitating disease characterized by irreversible destruction of alveolar tissue. This destruction results in reduced elastic recoil, progressive hyperinflation and gas trapping with patients experiencing chronic dyspnea, limited exercise tolerance and poor health related quality of life. In emphysematous COPD, diseased portions of the lung ventilate poorly, cause air trapping, and hyperinflate, compressing relatively normal lung tissue. The patterns and degree of emphysema heterogeneity (i.e., the extent and distribution of air space enlargements) can be measured using computed tomography (CT) density as an indicator for tissue destruction. The most diseased portions of lung can then potentially be targeted for lung volume reduction procedures. In homogeneous emphysema, there is minor or no regional difference in disease within or between lobes of the lung. Bronchial valves are synthetic devices deployed with bronchoscopy into ventilatory airways of the lung to control airflow. During inhalation, the valve is closed, preventing air flow into the diseased area of the lung. The valve can open during exhalation to allow air to escape from the diseased area of the lung. They have been investigated for use in patients who have prolonged bronchopleural air leaks and in patients with hyperinflation from severe or advanced emphysema.

When used to treat persistent air leaks from the lung into the pleural space, the bronchial valve theoretically permits less air flow across the diseased portion of the lung during inhalation, aiding in air leak closure. The valve may be placed, and subsequently removed by bronchoscopy. The use of bronchial valves to treat emphysema is based on the improvement observed in patients who have undergone lung volume reduction surgery. Lung volume reduction surgery involves excision of peripheral emphysematous lung tissue, generally from the upper lobes. The precise mechanism of clinical improvement for patients undergoing lung volume reduction has not been firmly established. However, it is believed that elastic recoil and diaphragmatic function are improved by reducing the volume of the diseased lung. Currently, and at the time the clinical trials were designed, very few lung volume reduction procedures were performed. The procedure is designed to relieve dyspnea and improve functional lung capacity and quality of life; it is not curative. Medical management remains the most common treatment for a majority of patients with severe emphysema.

In early trials of bronchial valves for treatment of emphysema, absence of collateral ventilation (pathways that bypass the normal bronchial airways) was associated with better outcomes, presumably because patients with collateral ventilation did not develop lobar volume reduction or atelectasis (collapse). In subsequent trials, patients were selected for absence of collateral ventilation, and it is current practice for patients to be assessed for the presence of collateral ventilation prior to undergoing the procedure. Collateral ventilation is measured by the Chartis system, which requires bronchoscopy, or as a surrogate, CT scanning to assess the completeness of fissures, SeleCT or StratX systems. After 45 days post-procedure, residual volume can provide information on whether lung volume reduction has been achieved successfully.

REGULATORY STATUS

Currently, two endobronchial valve systems are FDA-approved for treatment of patients with severe emphysema (FDA product code: NJK). Both are one-way valves which work to prevent air flow to the diseased area of the lung during inhalation. The valves allow air to escape from the treated lobe(s) during exhalation. In June 2018, the FDA granted the Zephyr® Endobronchial Valve (formerly Emphasys, now Pulmonx) system breakthrough device status with expedited approval for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation.[1] The Zephyr Endobronchial Valve (EBV) is a one-way, removable, silicone, duckbill valve mounted in a nitinol, self-expanding retainer that is covered with a thin silicone membrane. The valve is available in three sizes and implanted during bronchoscopy in bronchial lumens ranging from 4.0 to 8.5 mm in diameter. In December 2018, the FDA approved the Spiration® Valve System.[2] The Spiration® Valves are one-way endobronchial valves intended for adult patients with shortness of breath and hyperinflation associated with severe emphysema in regions of the lung that have low collateral ventilation. The Spiration® Valve System is deployed into the bronchial tree using the deployment catheter passed through the working channel of a flexible bronchoscope with working channel 2.6 mm or greater. The Spiration valves are provided in four sizes to accommodate airway diameters ranging from 4.75 to 8.75 mm. Both valves may require repeat procedures to reposition or restore functioning. Although more than one valve may be needed to achieve the desired clinical outcome, FDA safety testing assumed no more than 10 valves will be placed in a clinical procedure for the treatment of severe emphysema.

The intrabronchial IBV® Valve System (Spiration, Inc) was approved by the U.S. Food and Drug Administration (FDA) under the Humanitarian Device Exemption (HDE) number H060002. It is intended for use in controlling prolonged air leaks of the lung or significant air leaks that are likely to become prolonged air leaks following lobectomy, segmentectomy, or lung volume reduction surgery (LVRS), for a duration up to 6 weeks.[3]

EVIDENCE SUMMARY

PROLONGED OR SIGNIFICANT AIR LEAKS

The principal outcome associated with treatment of prolonged or significant air leaks include resolution of the leak. In order to understand the impact of bronchial valves for treatment of prolonged or significant air leaks, well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as chest tube placement, performing a thoracotomy with mechanical or chemical pleurodesis, or additional operations, are needed.[3]

Systematic Review

No systematic reviews (SRs) were identified on the use of endobronchial or intrabronchial valves for prolonged or significant air leaks.

Randomized Controlled Trials

No randomized controlled trials (RCTs) were identified on the use of endobronchial or intrabronchial valves for prolonged or significant air leaks.

Nonrandomized studies

No comparative observational studies were identified. Nonrandomized studies have reported on the use of either intrabronchial[4], endobronchial valves[5, 6], or both types[7]. Conclusions cannot be reached from of these studies, as the data are limited by a variety of factors, including but not limited to:

- Small study populations, less than 100 patients total, which limit the ability to rule out the role of chance as an explanation of study findings;[4, 5, 7] and
- Retrospectively abstracted records, leading to potential study bias in sample selection, including selection criteria.[5, 7]
- Follow-up of study subjects was over a short period of time, less than 6 months, so medium and long-term effects of endobronchial valves treatment are unknown.[4, 5, 7]

ADVANCED EMPHYSEMA

In patients with advanced emphysema, valves may be compared to other forms of medical treatment, such as bronchodilators, short courses of systemic corticosteroids, noninvasive positive pressure ventilation (NIPPV) and/or oxygen therapy. In patients who have exhausted conservative therapy, valves must be compared to more invasive treatment, such as lung volume reduction surgery. RCTs are needed in order to isolate the contribution of these implants from other components of therapy. Further, for treatment of chronic conditions, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits to understand the net treatment effect.

Systematic Reviews

A 2020 systematic review (SR) with network meta-analysis by Iftikhar evaluated the effect of bronchial valves in patients with heterogeneous emphysema without lobar collateral ventilation (CV).[8] The review included 10 RCTs studying adult COPD patients with severe emphysema on optimal medical management and undergoing intervention with Zephyr or Spiration valves or coils for the intervention and standard of care as the comparator. A total of 912 total study participants (544 in intervention arms and 368 in control arms) were included in the meta-analysis. No statistical evidence of funnel plot asymmetry (or publication bias) was found. In patients with heterogeneous emphysema without CV, both Spiration and Zephyr valves showed significant increases in forced expiratory volume in 1 second (FEV1) (0.11 L [95% confidence interval (CI), 0.05 to 0.16] and 0.14 L [0.08 to 0.19], respectively) and in reducing St. Georges Respiratory Questionnaire (SGRQ) scores (-9.32 [-14.18 to -4.45] and -8.14 [-11.94 to -4.35], respectively) as compared with control, with no significant differences between interventions. Significant improvement (52.3 m [95% CI, 26.53 to 77.93]) in six-minute walk distance (6MWD) also was found for Zephyr valves, specifically. Both Spiration and Zephyr valves were associated with more frequent pneumothorax as compared with control (odds ratio, 10.32 [1.35 to 79.13] and 11.47 [2.91 to 45.27], respectively). No statistically significant association for COPD exacerbations was found for any of the interventions.

Majid (2020) published a systematic review (SR) with meta-analysis of four RCTs (N= 629) evaluating the Spiration® Valve System (SVS) in patients with severe emphysema and hyperinflation.[9] The RCTs included were published by Ninane (2012),[10] Wood (2014),[11] Li (2019),[12] and Criner (2019).[13] Outcomes evaluated were changes in: forced expiratory volume in 1s (FEV1), 6-min walking test (6MWT), residual volume, modified medical research council (mMRC) and Saint George respiratory questionnaire (SGRQ), as well as all-cause mortality, risk of pneumothorax, and risk of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). An overall change of 0.03 L (-0.07 to 0.13, I^2 = 90%) in FEV1 and 2.03% (-2.50 to 6.57, I^2 = 96%) in the predicted FEV1 compared to baseline was found with SVS but no benefit in 6MWT (mean difference = 4.56 m [95% CI -21.88 to 31.00, I^2 =

73%]). Relative risk of mortality was 2.54 (95% CI 0.81-7.96, I^2 = 0%), for pneumothorax 3.3 (95% CI 0.61-18.12, I2 = 0%) and AECOPD 1.68 (95% CI 1.04-2.70, I^2 = 0%). In patients with severe heterogeneous emphysema and hyperinflation without collateral ventilation, treatment with SVS improved pulmonary function, quality of life, and dyspnea score. However, the significantly increased relative risk of adverse events, including mortality, warrants additional RCTs addressing the safety and long-term benefit of this treatment.

In a SR with network meta-analysis by Xu (2020), bronchoscopic lung volume reduction treatments for emphysema, including intrabronchial valve (IBV) and endobronchial valve (EBV) treatments, were evaluated.[14] Thirteen trials were included (N=1993), seven of which were on IBV or EBV, including some studies reported in previous SRs.[15-19] The quality of evidence was rated as moderate in most comparisons using the GRADE framework. Medical care (MC) was associated with the fewer adverse events than IBV (-2.5, [-4.70 to -0.29]) and EBV (-1.73, [-2.37 to -1.09]) treatments. Less of an improvement in FEV1 and 6MWT was found in MC compared with EBV (-0.45, [-0.69 to -0.20] and -0.39, [-0.71 to -0.07], respectively) and significantly more positive change in SGRQ was found in EBV compared with MC (0.44, [0.11 to 0.78]). This analysis provides important comparisons of bronchial valve treatments to medical care alone for emphysema. Although clinical and quality of life variables improved with valve treatment, more adverse events occurred with both IBV and EBV treatment compared to MC alone, which is consistent with other systematic reviews evaluating safety of these devices.

A SR with meta-analysis published by Low (2019) evaluated RCTs comparing EBV implantation versus standard medical treatment or sham bronchoscopy for advanced emphysema.[20] This SR included five RCTs (N= 703) published by Valipour (2016)[21], Sciruba (2010)[22], Klooster (2015),[23] Herth (2012),[19] and Davey (2015).[15] Across these studies, the percentage change of FEV1 was significantly improved in the EBV group compared with the control group [weighted mean difference (WMD)=11.43; 95% confidence interval (CI), 6.05-16.80; P<0.0001] as was the SGRQ score (WMD=-5.69; 95% CI, -8.67 to -2.70; P=0.0002). No group difference was found in the 6MWT (WMD=14.12; 95% CI, -4.71 to 32.95; P=0.14). There was an increased rate of pneumothorax [relative risk (RR)=8.16; 95% CI, 2.21-30.11; P=0.002), any hemoptysis (RR=5.01; 95% CI, 1.12-22.49; P=0.04)] and valve migration (RR=8.64; 95% CI, 2.01-37.13; P=0.004) in the EBV group. Although there were short-term improvements in lung function and quality of life observed with the EBV, the significant increases in complication rates demonstrate the need for additional studies to determine the long-term safety and effectiveness of the treatment.

La Barca (2019) published a SR with meta-analysis of RCTs evaluating the efficacy and safety of the Zephyr® valve.[24] Seven RCTs reported on Zephyr® valves and five RCTs included only patients without collateral ventilation. Outcomes evaluated were change in: FEV1, 6MWT, SGRQ, and in residual volume (RV). Safety analysis included relative risk (RR) of pneumothorax. Treatment with the Zephyr® valve improved FEV1 with a mean difference (MD) of 17.36% (CI, 9.28-25.45, I2 = 78%). Subgroup analysis showed significant FEV1 improvement following Zephyr® placement in patients with heterogeneous distribution: MD = 21.78% (CI, 8.70-34.86, I^2 = 89%) and 16.27% (CI, 8.78-23.76, I^2 = 0%) in patients with homogeneous emphysema. Follow-up of 6-12 months showed a consistent improvement of FEV1 MD = 17.90% (CI, 11.47-24.33, I2 = 0%). Despite these positive clinical outcomes, the relative risk of pneumothorax was 6.32 (CI, 3.74-10.67, I2 = 0%). While this SR found clinically meaningful improvements with Zephyr® valve, there also was a significant increase in adverse events with the device. These conclusions are consistent with a comprehensive review of lung volume reducing surgical and endoscopic interventions for emphysema published by van Geffen (2019) that also included seven RCTs of the Zephyr® valve.[25] Five of the studies are included in Table 1 under Endobronchial Valve Studies, and the additional two are LIBERATE[26, 27] and TRANSFORM[28]. Participants in the included studies were those with emphysema, older than 35 years, post-bronchodilator FEV1 < 60% of predicted, and residual volume >150% of predicted (N = 620 total, range per study varied 50-190). Studies lasted from 3-12 months in duration. Meta analyses found adverse events including mortality to be greater in those who received valves: OR 9.58 (5.56 to 16.50), p=<0.00001.

A 2017 SR with meta-analysis by Wang evaluated bronchoscopic lung volume reduction therapy in patients with severe emphysema which included six RCTs for EBVs and two RCTs for IBVs.[29] Better response in minimal clinically important difference (MCID) was found in EBV trials for FEV1 (RR = 2.96, 95% CI = 1.49 – 5.87, p = 0.002, I2 = 58%), for 6MWT (RR = 2.90, 95% CI = 1.24 – 6.79, p = 0.01, I2 = 80%), for SGRQ (RR = 1.53, 95% CI = 1.22 – 1.92, p = 0.0002, I2 = 0%), as well as for mMRC (RR = 2.53, 95% CI = 1.71 – 3.76, p <0.00001, I2 = 0%). Similarly, EBV therapy was associated with significant improvement in ΔFEV_1 (WMD = 11.44%, 95% CI = 6.11 – 16.77, $p < 0.0001$, $I^2 = 57\%$), in Δ6WMT (WMD = 33.86m, 95% CI = 11.54 – 56.19, $p = 0.003$, $I^2 = 76\%$), and in ΔSGRQ (WMD = -7.06 points, 95% CI = -10.71 – -3.41, $p = 0.0001$, $I^2 = 63\%$), in ΔmMRC (WMD = -0.35 point, 95% CI = -0.56 – -0.14, $p = 0.0008$, $I^2 = 30\%$). The IBV group was not found to be superior to the conventional group. No sub-analysis was provided for emphysema type (homogenous vs. heterogenous).

In 2017, a Cochrane Systematic Review evaluating bronchoscopic lung volume procedures for COPD was published by van Agteren.[30] Authors conducted in-depth analyses aimed at assessing the effects of bronchoscopic lung volume reduction procedures on the short- and long-term health outcomes in participants with moderate to severe COPD and determining the effectiveness of each technique. Endobronchial and intrabronchial valves were among the six techniques analyzed; only individually and cluster randomized controlled trials were included. See Table 1 for endobronchial and intrabronchial valve studies included for analyses. Studies including participants with giant or bullous emphysema were excluded. Primary outcomes included: lung capacity as measured by FEV1; survival as measured by perioperative and postoperative mortality; and health-related quality of life, measured by questionnaire (e.g., St Georges Respiratory Questionnaire [SGRQ]). Given the heterogeneity in treatment approaches, outcomes were meta-analyzed only per treatment type. Outcomes for continuous or dichotomous data were analyzed using a fixed-effect model up to the end of follow-up. Continuous outcomes were calculated using mean differences, and dichotomous outcomes with odds ratios, both with 95% confidence intervals. Heterogeneity was calculated using the I^2 statistic, and subgroup analysis was performed as appropriate. Studies were graded for bias as high, low, or unclear, with rationale reported. Quality of evidence was rated using the GRADE scale. EBV and IBV studies included both heterogenous and homogeneous disease status patients, though majority of the EBV studies included participants with only a heterogenous disease distribution. The average of participants ranged between 58 and 65 years of age; the STELVIO 2015 trial having the youngest average age (58 to 59 years of age); the IBV Valve Trial 2014 and the VENT US 2010 studies having the highest average age ranging between 64.7 and 64.8, and 64.9 and 65.3, respectively. Majority of the trials recruited more males than females.

Table 1. RCTs included in 2017 Cochrane Review

Endobronchial Valve Studies (Year)	Intrabronchial Valve Studies (Year)
BeLieVeR HIFi (2015)[15, 31]	Eberhardt (2012)[32]

Endobronchial Valve Studies (Year)	Intrabronchial Valve Studies (Year)
IMPACT (2016)[21]	IBV Valve Trial (2014)[11]
STELVIO (2015)[23, 33]	Ninane (2012)[10]
VENT EU (2012)[19]	
VENT US (2010)[22, 34-39]	

Endobronchial Valves

The conclusions from the EBV studies were drawn from five studies totalling 703 participants, which used standard medical care as the comparator. The results from the Cochrane SR by van Agteren are consistent with the subsequent SRs noted above. The number of adverse events experienced by patients with endobronchial valves was higher than those who received standard medical treatment (OR [95% confidence interval], 5.85 [2.16, 15.84], high quality of evidence), though no significant difference in mortality was found. From baseline to follow-up, between-group differences in the EBV group compared to control, change in lung function (FEV1, standardized mean difference [SMD], of 0.48 [95% CI: 0.32 to 0.64], low-quality evidence), quality of life (mean difference [MD], -6.20 units [95% CI: -8.19 to -4.20]; low quality of evidence), and exercise capacity (38.40 meters [95% CI: 24.69 to 52.12]; low quality of evidence) were significantly improved. While positive results may have been found, due to high confidence intervals and standard deviations, the authors urged caution in interpreting the means reported for outcomes of their systematic review. Earlier trials found better outcomes in patients with intact fissures which affected selection criteria in future trails, and thus improvement in functional outcomes.

Intrabronchial Valves

Two RCTs comparing intrabronchial valves to standard medical treatment were included for review,[10, 11] as well as one trial comparing unilateral versus partial bilateral valve placement with intrabronchial valves[32]. Adverse events experienced by patients with intrabronchial valves was higher than those who received standard medical treatment (OR, 3.41 [1.48, 7.84]), and no significant risk in mortality. Between group difference in exercise capacity was found to favor controls (MD -19.54 meters; [95% CI -37.11 to -1.98], moderate-quality evidence), as did lung function. Lack of difference in the IBV Valve trials by Wood (2014) and Ninane (2012) may be explained by the Eberhardt (2012) trial, as the latter found those treated with unilateral valve placement as opposed to partial bilateral treatment showed significantly better results in lung function, quality of life, and exercise capacity. The other two trials did not specifically address collateral ventilation, nor did they aim to achieve lobar occlusion; this is supported by the EBV trials which all aimed to achieve lobar occlusion and found better functional results when achieved.

Overall, findings in the Cochrane meta-analyses are limited by the lack of long-term follow-up data, significant heterogeneity in results, presence of skew and high CIs, and the open-label character of a number of the studies.

Choi (2015) published a systematic review evaluating bronchoscopic lung volume reduction using a one-way endobronchial valve.[40] The systematic review included 15 studies and meta-analyzed RCTs. Forced expiratory volume in one second (FEV1) improved compared to control groups in favor of the valve group (mean difference of 6.71, 95% CI: 3.31-10.11). The six-minute walking distance and cycle workload were also improved. A subgroup analysis of patients with complete fissure, reported that the FEV1 change was higher in the valve group at six and 12-months compared to the control group. No deaths were reported for the bronchial valve group although the pneumothorax incidence and respiratory failure rates were higher in the EBV group.

Randomized Controlled Trials

RCTs not included in the above-described systematic reviews are summarized here.

Gompelmann (2019) published long-term follow-up data on patients with severe emphysema with no collateral ventilation treated with endobronchial or intrabronchial valves.[41] Of the 256 patients, 220, 200, 187, 100 and 66 patients completed the three-month, six-month, one-year, two-year and three-year follow-up visit, respectively. Lung function parameters [FEV1, vital capacity (VC), residual volume (RV), total lung capacity (TLC)] and exercise capacity [6-minute walk test (6-MWT)] were outcomes evaluated. Response rates were calculated as the number of patients who met the minimal important difference (MID) of >100 ml improvement in FEV1, >430 ml reduction in RV and >26 m improvement in 6-MWT. Patients who underwent further interventional strategies (LVRS, coil therapy, polymeric lung volume reduction, lung transplantation) within the observation timeframe were excluded after the additional therapeutic intervention. At six-month follow-up, 37% of the patients met the efficacy threshold of greater than 100 ml improvement in FEV1, 78% of the patients developed a greater than 430 ml reduction in RV and 58% of the patients experienced a greater than 26 m improvement on the 6-MWT. At one-year follow-up, significant improvement from baseline ($p<0.05$ in paired t-tests, uncontrolled for repeated observations) was found for lung function parameters including FEV1 and RV and exercise capacity (6-MWT). At three-year follow-up (n=66), the proportion of patients achieving the MID from baseline in RV and 6-MWT was 71% and 46%, respectively. Radiological follow up was assessed in 251 of the patients, and of these, 22% (56/251) developed a pneumothorax. Management of pneumothorax was via chest tube insertion in 86% (48/56) of these patients, and in 41% (23/56), valve removal was necessary for pneumothorax management. Over the three-year observation, all valves were permanently removed in 24.6% (63/256) of the patients. Permanent valve removal was conducted due to the following reasons: missing clinical benefit in 55.6% (35/63), pneumothorax in 11.1% (7/63), definitive LVRS in 19% (12/63), poststenotic pneumonia in 6.3% (4/63), lung cancer in 3.2% (2/63), respiratory insufficiency in 3.2% (2/63) and recurrent pulmonary infections in 1.6% (1/63). No analyses specific to endobronchial versus intrabronchial valve use was provided. This trial is limited by the lack of a comparative group such as medical management alone and by the retrospective design, as well as considerable loss to follow-up. Despite these limitations, this study provides important data regarding longer-term outcomes for highly-selected patients undergoing endobronchial valve treatment for severe emphysema and indicate clinically meaningful improvement can be achieved in these selected patients.

In 2017, Klooster reported one-year follow-up data from the STELVIO study not included in the SRs above.[42] An intention-to-treat analysis showed greater improvements in all primary outcomes in the EBV group compared to the controls. However, of the 64 patients with follow-up data available, 47 serious adverse events were reported from 0-6 mos, and 11 from 6 mos to one year. Two patients in the valve group died.

Nonrandomized Studies

A retrospective review of 1500 patients with severe COPD referred for bronchoscopic lung volume reduction (BLVR) treatment was conducted by Welling (2020) to investigate the differences between patients selected for BLVR and patients that were not.[43] Of those reviewed, 282 (19%) patients were selected for BLVR treatment, and of these, 175 patients

(62%) were selected for EBV, 93 patients (33%) for lung volume reduction coil (LVRC), three patients (0.2%) for airway bypass stents, nine patients (3%) for polymeric lung volume reduction and two patients (0.1%) for a pneumostoma. Although the authors found that patients who were selected for any BLVR option lived significantly longer than those who were not selected for BLVR (median 3060 versus 2079 days, p<0.001), these patients also were significantly younger (59 versus 63 years), had a lower FEV1 (28% versus 34% of predicted) and a higher residual volume (237% versus 215% of predicted) compared to the group of patients not selected for BLVR (all p<0.001). No significant survival difference was observed between patients who were selected for EBV treatment and those who were selected for LVRC (p=0.45).

Skowasch (2016) reported six month follow-up results from the VENT trial, a retrospective analysis of registry data for patients who have received endobronchial valves also described below.[44] Although lung function (FEV1 and residual volume), and COPD Assessment Test scores improved, 66 serious adverse events were reported in 55 patients. In the subsequent six months of follow-up, a total of 170 serious adverse events were reported in 125 patients.

Liberator (2016) published a retrospective analysis of the VENT trial.[37] The analysis evaluated outcomes and response based on lobe selection in patients receiving EBV therapy. The authors concluded that lobe selection does have a major role in EBV therapy. There was no difference in FEV1 outcomes between upper and lower lobe treatment groups. The authors further conclude that complete fissure status preprocedure has the greatest influence on FEV1 outcome improvement.

Several other small case series (n<100) have been published on the use of the Zephyr or IBV valves for severe emphysema.[18, 33, 45-49] The ability to draw conclusions based on these data is limited by a variety of factors, including small sample sizes, limited long-term follow-up data, and heterogeneity in study design including patient inclusion criteria and varying numbers of valves placed per patient. For example, a mean of four (SD: 1.6) and range of 1-8 in one study[50] and a mean of 6.7 and range of 3-11 in the other[45], and unreported mean and range in the third[47, 48], limiting comparisons of treatment effectiveness.

Section Summary: Advanced Emphysema

In patients with severe emphysema and low collateral ventilation, RCTs provide consistent evidence of clinically meaningful benefit for endobronchial valves compared to standard medical management on measures of lung function and quality of life. Systematic review of the available evidence also finds significant improvement in clinical and functional outcomes in select patients treated with endobronchial valves compared to standard medical management. Systematic review of the current evidence also indicates there is a greater risk of serious adverse events compared to usual care, including mortality and pneumothorax.

PRACTICE GUIDELINE SUMMARY

The 2021 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report on the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease makes the following statements on lung volume reduction interventions:[51]

- In selected patients with heterogeneous or homogeneous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of

lung volume reduction (e.g., endobronchial one-way valves, lung coils, or thermal ablation) may be considered.
- In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment (Evidence Level A for endobronchial valves: well-designed RCTs with consistent findings in the intended population without any important limitations).

NICE guidance on the diagnosis and management of COPD (2018) included the following recommendations on lung volume reduction procedures:[52]

> Offer a respiratory review to assess whether a lung volume reduction procedure is a possibility for people with COPD when they complete pulmonary rehabilitation and at other subsequent reviews, if all of the following apply:
>
> - they have severe COPD, with FEV1 less than 50% and breathlessness that affects their quality of life despite optimal medical treatment
> - they do not smoke
> - they can complete a 6-minute walk distance of at least 140 m (if limited by breathlessness).
>
> At the respiratory review, refer the person with COPD to a lung volume reduction multidisciplinary team to assess whether lung volume reduction surgery or endobronchial valves are suitable if they have:
>
> - hyperinflation, assessed by lung function testing with body plethysmography and
> - emphysema on unenhanced CT chest scan and
> - optimized treatment for other comorbidities.
>
> For more guidance on lung volume reduction procedures, see the NICE interventional procedures guidance on lung volume reduction surgery, endobronchial valves.

In December 2017, the National Institute for Health and Care Excellence (NICE) issued the following recommendations on EBV insertion to reduce lung volume in emphysema:[53] .

- Current evidence on the safety and efficacy of EBV insertion to reduce lung volume in emphysema is adequate in quantity and quality to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.
- Patient selection should be done by a multidisciplinary team experienced in managing emphysema, which should typically include a chest physician, a radiologist, a thoracic surgeon and a respiratory nurse.
- Patients selected for treatment should have had pulmonary rehabilitation.
- The procedure should only be done to occlude volumes of the lung where there is no collateral ventilation, by clinicians with specific training in doing the procedure.

SUMMARY

There is enough research to show that bronchial valves improve net health outcomes (balance of benefit and harm) compared to current standard of care for highly selected patients with advanced emphysema. Clinical guidelines based on research recommend endobronchial valves in the treatment of advanced emphysema for select patients. Therefore, US Food and Drug Administration (FDA) – approved endobronchial valve placement may be considered medically necessary for the treatment of advanced emphysema when policy criteria are met.

Removal, replacement, or revision of bronchial valves placed for the treatment of severe emphysema may be required after the device has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device or removal may be appropriate when the condition of the patient has changed. Therefore, revision, replacement, or removal of an existing US Food and Drug Administration (FDA) – approved endobronchial valve may be considered medically necessary after the device has been placed.

There is not enough research to show that bronchial valves improve net health outcomes (balance of benefit and harm) compared to current standard of care for any indication other than for the treatment of severe emphysema when criteria are met. Clinical guidelines based on research recommend bronchial valves only in select patients. Therefore, bronchial valve placement is considered investigational for all indications other than for the treatment of severe emphysema when policy criteria are met, including for the treatment of air leaks and for the treatment of emphysema when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	31647	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe
	31648	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe
	31649	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure)
	31651	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure[s])
HCPCS	None	

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