Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual

Topic: Endobronchial Valves

Date of Origin: February 2012

Section: Surgery

Approved Date: April 2014

Policy No: 184

Effective Date: July 1, 2014

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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).

Endobronchial valves are synthetic devices that are deployed with bronchoscopy into ventilatory airways of the lung for the purpose of controlling airflow. During inhalation the valve is closed preventing air flow to the diseased area of the lung. The valve opens during exhalation to allow air to escape from the diseased area of the lung. The valve may be placed, and subsequently removed, by bronchoscopy. These devices had been proposed for use in two patient populations:

- Patients with prolonged or significant (≥ 5 days or more) air leaks. When used to treat persistent air leak from the lung into the pleural space, the endobronchial valve theoretically permits less air flow across the diseased portion of the lung during inhalation, aiding in air leak closure. Endobronchial valves have been proposed as a more effective intervention for use in prolonged or significant air leaks where current treatment options have not been effective.

- Patients with advanced emphysema. In advanced emphysema, peripheral lung tissue may form bullae, causing air trapping, and hyperinflation, which compresses relatively normal lung tissue. Use of an endobronchial valve is thought to prevent hyperinflation of these bullae.

Currently, lung volume reduction surgery (LVRS) is the standard of care for patients with advanced emphysema. LVRS involves excision of peripheral emphysematous lung tissue, generally from the upper lobes. The procedure is designed to relieve dyspnea and improve functional lung capacity and quality of life; however, it is not curative. Because only a subset of patients with advanced emphysema qualify for LVRS, and among those who have the surgery, mortality rates are higher than medical management alone[1], endobronchial valves have been proposed as a safer and more accessible alternative to LVRS.

Regulatory Status

Two endobronchial valve devices have been considered by the U.S. Food and Drug Administration (FDA), but approval has only been granted for one device, the IBV® Valve System (Spiration, Inc). This device was approved under the Humanitarian Device Exemption (HDE) 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. Use in patients with advanced emphysema has also been investigated as an off-label indication.[2]

The Zephyr® Endobronchial Valve (formerly Emphasys, now Pulmonx) was considered by the Anesthesiology and Respiratory Therapy Device Panel for use as a permanent implant in patients with severe, heterogeneous emphysema who have received optimal medical management. However, the panel declined to recommend the device for FDA approval.

MEDICAL POLICY CRITERIA

I. Endobronchial valves are considered **investigational** as a treatment of prolonged air leaks.

II. Endobronchial valves are considered **investigational** as a treatment for patients with COPD or emphysema.

SCIENTIFIC EVIDENCE

The principal outcome associated with treatment of prolonged or significant air leaks include resolution of the leak. In order to understand the impact of endobronchial 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.[2]

In patients with advanced emphysema, endobronchial 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, endobronchial valves must be compared to more invasive treatment, such as lung volume reduction surgery. Randomized studies 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.

Literature Appraisal

Prolonged or Significant Air Leaks

No randomized controlled trials (RCTs) or comparative observational studies were identified on the use of endobronchial valves for treatment of prolonged or significant air leaks. Several nonrandomized studies have been published.

Nonrandomized studies

Three case series reported on the use of endobronchial valves for the treatment of air leaks, one on the IBV[3], one on the Zephyr[4] and one study which used both valves.[5]

Conclusions cannot be reached from either 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;[3-5] and
- Retrospectively abstracted records, leading to potential study bias in sample selection, including selection criteria.[4,5]
- 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.[3-5]

Conclusion

The only available data on endobronchial valves for treating persistent air leaks are uncontrolled trials with small numbers of heterogenous patients. Therefore, the evidence is not adequate to determine the impact of this technology on the net health outcome, nor does it provide any evidence on comparisons with alternative treatment of air leaks.

Advanced Emphysema

The published literature consists of one RCT and several nonrandomized studies on the Zephyr valve and one nonrandomized study on the IBV valve.

Randomized Controlled Trial (RCT)

The Endobronchial Valve for Emphysema Palliation Trial (VENT) was an industry-funded open-label RCT which collected data at 31 centers in the United States.[6,7] Key eligibility criteria were: diagnosis of heterogeneous emphysema, forced air expiratory volume in 1 second (FEV1) of 15-45% of the predicted value, total lung capacity of more than 100% of the predicted value, residual volume of more than 150% of the predicted value, and post-rehabilitation 6-minute walk distance of at least 140 meters. A total of 321 patients were randomly assigned on a 2:1 basis to receive Zephyr endobronchial valves (n=220) or standard medical care (n=101). The mean number of valves placed in the endobronchial

valve group was 3.8 per patient (range, 1 to 9). The primary effectiveness outcomes were percent change from baseline to 6 months in the FEV1 and distance on the 6-minute walk test.

Following are the findings from this study:

- Primary outcomes data at 6 months indicated a slight advantage for the group with endobronchial valves versus the control group in mean FEVI and median distance on 6-minute walk test. Secondary outcomes, relating to quality of life, showed statistically significant improvement among the treatment versus control groups, though the difference (less than 4 points on the St. George's Respiratory Questionnaire [SGRQ]), was not clinically meaningful.[8] Other differences in secondary outcomes, relating to mean change in total lung volume, residual volume and inspiratory capacity were not statistically significant.

- The rate of 6 major complications (death, empyema, massive hemoptysis, pneumonia distal to valves, pneumothorax or air leak of more than 7 days' duration or ventilator-dependent respiratory failure for more than 24 hours), was slightly higher in the treatment versus control groups, though the difference was not significant. Adverse events to 6 months included 6 deaths (2.8%) in the endobronchial valve group and no deaths in the control group (p=0.19).

- In 2012, Herth and colleagues reported on 171 additional patients who participated in the European cohort of the VENT study.[9] Similarly, patients were randomly assigned on a 2:1 basis to receive Zephyr endobronchial valves (n=111) or standard medical care (n=60). A total of 154 of 171 (90%) patients completed the 6-month follow-up and 136 of 171 (80%) completed the 12-month follow-up. Data on the 6-minute walk test at 12 months and findings on the composite safety variable were not reported.

  Serious complications and the rate of COPD exacerbations did not differ significantly between groups, and there were no reported cases of emphysema or massive hemoptysis. Five cases of pneumothorax requiring hospitalization for longer than 7 days were reported in the endobronchial valve group. There were 10 deaths, 6 in the endobronchial valve group and 4 in the control group; none were considered to be related to study procedures. Over the 12-month follow-up period, there were 13 cases of valve expectoration, aspiration or migration; this represented 12% of the 111 patients in the endobronchial valve group. Eight out of 13 events occurred in the first 90 days after valve placement.

- In 2013, Valipour and colleagues combined results from the US and European cohorts and reported on those in both the treatment (n=284) and control (n=132) groups who received follow-up computed tomography scans at 6 month follow-up.[10] An intention-to-treat approach was used and the authors reported that mean target lobar volume reduction was significantly higher in patients receiving endobronchial valve therapy than in control patents (-242 mL vs 0.5 mL, p<0.001). Moreover, 42% of patients in the endobronchial valve group and 24.7% of controls had improvement of at least 1 point in the BODE index at 6 months (p<0.001). (The BODE index combines several variables, including the FEV1 and the distance on the 6-minute walk test. A higher score on the BODE index has been found to correlate with an increased risk of death from COPD). Valipour et al did not discuss missing data on the FEV1 or 6-minute walk test measures at 6 months. In addition, these outcomes were not originally listed as primary or secondary outcome measures in the original study.[6,7]

A limitation of the original study was a lack of blinding, which could have affected performance on the primary efficacy outcomes, e.g., it may have affected clinicians' coaching of patients and/or the degree of effort exerted by patients. Additionally, between the two VENT publications, 20% of the European cohort and 28% of the U.S. cohort primary efficacy outcomes data were missing, indicating significant potential for bias in results. Although there was a pre-specified plan for handling missing data, with this degree of data missing, findings might not accurately represent outcomes in the population. Moreover, although Herth and colleagues reported that the study had sufficient statistical power, there tended to be wide confidence intervals, indicating an insufficiently large sample size. Also, some between-group differences in primary outcomes, though statistically significant, may not be clinically relevant, e.g., a 7-8% difference in absolute change from baseline in FEV1.

An editorial review of the first trial publication noted that the rate of complications, such as COPD, were higher in the endobronchial valve group, albeit not statistically different.[11] The editorial additionally criticized the study for not standardizing medical treatment for the control group and for possibly providing suboptimal medical therapy for both groups, e.g., only 57% of patients received recommended bronchodilators at the beginning of the study, and that the medical therapy was not standardized.

Nonrandomized Studies

Several reports on three small case series (n<100) have been published on the use of the Zephyr or IBV endobronchial valves for severe emphysema.[12-15] Varying numbers of endobronchial valves were placed per patient and follow-up time ranged from 3 months up to 8 years.

Conclusions based upon this data are limited by a variety of factors, including but not limited to:

- Small study populations, less than 100 patients total,[12-15] limit the ability to rule out the role of chance as an explanation of study findings.
- Follow-up of study subjects was over a short period of time, less than 6 months,[11] so medium and long-term effects of endobronchial valves treatment are unknown.
- Varying numbers of valves were placed per patient: a mean of 4 (SD: 1.6) and range of 1-8 in one study[11] and a mean of 6.7 and range of 3-11 in the other[12], and unreported mean and range in the third[14,15], limiting comparisons of treatment effectiveness.
- Patient selection criteria differed, along with use of medication, hampering comparisons of target population and exposure of interest.[12-15]

Although adverse events are not systematically reported in the literature on endobronchial valves, in one report, 38 of 98 patients (39%) treated with endobronchial valves developed a complication following this procedure, ranging from exacerbation of chronic obstructive pulmonary disease to death.[12]

Conclusion

For patients with advanced emphysema, case series and a single unblinded RCT provide insufficient evidence that the technology improves the net health outcome compared to standard of care treatments. Although statistically significant change in FEV1 and in the 6-minute walk distance from baseline to 6 months in the U.S. cohort and a statistically significant change in FEV1 at 12 months in the European cohort were reported in the single RCT, the magnitude of these improvements was of uncertain clinical significance. In addition, the numerous adverse events experienced by patients who received endobronchial valves raise concerns about the safety of the treatment.

Clinical Practice Guidelines

A search of the National Guideline Clearinghouse database and the websites of the American College of Chest Physicians and American Thoracic Society did not identify any relevant clinical guidelines or position statements recommending the use of endobronchial valves.

Summary

Based on the lack of published long-term objective outcomes from well-designed, well-executed randomized controlled clinical trials, conclusions cannot be reached concerning the effectiveness of endobronchial valves as a therapy for patients with air leak or advanced emphysema; therefore endobronchial valves are considered investigational for all indications. Larger, randomized controlled trials of longer duration are needed to evaluate the effectiveness of endobronchial valves in sealing air leaks, improving functional lung capacity and enhancing quality of life, and to determine whether endobronchial valves offer any additional benefit compared with other standard treatments.

REFERENCES

1. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med*. 2001 Oct 11;345(15):1075-83. PMID: 11596586
2. U.S. Food and Drug Administration. IBV® Valve System. Summary of safety and probable benefit. [cited 3/21/2012]; Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf6/H060002b.pdf
3. Gillespie, CT, Sterman, DH, Cerfolio, RJ, et al. Endobronchial valve treatment for prolonged air leaks of the lung: a case series. *Ann Thorac Surg*. 2011 Jan;91(1):270-3. PMID: 21172529
4. Travaline, JM, McKenna, RJ, Jr., De Giacomo, T, et al. Treatment of persistent pulmonary air leaks using endobronchial valves. *Chest*. 2009 Aug;136(2):355-60. PMID: 19349382
5. Firlinger, I, Stubenberger, E, Muller, MR, Burghuber, OC, Valipour, A. Endoscopic one-way valve implantation in patients with prolonged air leak and the use of digital air leak monitoring. *Ann Thorac Surg*. 2013 Apr;95(4):1243-9. PMID: 23434254
6. Sciurba, FC, Ernst, A, Herth, FJ, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med*. 2010 Sep 23;363(13):1233-44. PMID: 20860505
7. Sciurba, FC, Ernst, A, Herth, FJ, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med*. 2010;363(13):esupplement. PMID: No PMID Entry
8. Jones, PW, Quirk, FH, Baveystock, CM. The St George's Respiratory Questionnaire. *Respir Med*. 1991 Sep;85 Suppl B:25-31; discussion 3-7. PMID: 1759018
9. 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 Jun;39(6):1334-42. PMID: 22282552
10. Valipour, A, Herth, FJ, Burghuber, OC, et al. Target lobe volume reduction and COPD outcome measures after endobronchial valve therapy. England, 2014. p. 387-96.
11. Anzueto, A. Endobronchial valves to reduce lung hyperinflation. *N Engl J Med*. 2010 Sep 23;363(13):1280-1. PMID: 20860512
12. Wan, IY, Toma, TP, Geddes, DM, et al. Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. *Chest*. 2006 Mar;129(3):518-26. PMID: 16537847
13. Sterman, DH, Mehta, AC, Wood, DE, et al. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration*. 2010;79(3):222-33. PMID: 19923790

14. Hopkinson, NS, Toma, TP, Hansell, DM, et al. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *Am J Respir Crit Care Med*. 2005 Mar 1;171(5):453-60. PMID: 15579725
15. Hopkinson, NS, Kemp, SV, Toma, TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *Eur Respir J*. 2011 Jun;37(6):1346-51. PMID: 20947683
16. BlueCross BlueShield Association Medical Policy Reference Manual "Endobronchial Valves." Policy No. 7.01.128

CROSS REFERENCES

None

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	