Original Article

Off-label use of intrabronchial valves for persistent air leak is safe and effective: a retrospective case analysis

Harpreet Singh[1]^, Jonathan S. Kurman[1], Chinmay Jani[2,3], Mohammed Abdalla[1], Brandon DePaul[4], Bryan S. Benn[1]

[1]Department of Pulmonary and Critical Care, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [2]Department of Medicine, Mount Auburn Hospital, Cambridge, MA, USA; [3]Harvard Medical School, Boston, MA, USA; [4]Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Contributions: (I) Conception and design: JS Kurman, BS Benn, H Singh; (II) Administrative support: JS Kurman, BS Benn, H Singh; (III) Provision of study materials or patients: BS Benn, JS Kurman; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Harpreet Singh, MD. Medical College of Wisconsin, 8701 W Watertown Plank Road, Milwaukee, WI 53226, USA.
Email: hasingh@mcw.edu.

Background: Persistent air leak (PAL) is a challenging clinical problem associated with prolonged hospital stay and increased morbidity. Historically, treatment options were limited to thoracostomy tube drainage, pleurodesis, and surgical repair. The development of one-way airway valves has represented a paradigm shift in PAL management. We present our experience using intrabronchial valves (IBVs) for PAL management looking at both on-label (post-thoracic surgery) and off-label (all other) indications.

Methods: We performed a retrospective review of our single-center experience. Data collected included demographics, primary pathology leading to PAL, comorbidities, time to chest tube removal, complications, mortality, need for any additional procedure, and time to IBV removal.

Results: During the study period, 15 patients underwent IBV insertion for PAL. The on-label cohort contained three patients (post lobectomy or segmentectomy). The off-label cohort had 12 patients (6 empyema, 4 secondary spontaneous pneumothorax, 1 penetrating trauma, and 1 post percutaneous lung nodule biopsy). In the on-label cohort, chest tube was removed after a mean duration of 4.0±1.0 days for all patients. In the off-label cohort, 83.3% (10/12) had chest tube removal 16.2±5.7 days (P=0.396) after IBV placement. One patient developed hypoxic respiratory failure shortly after IBV insertion, necessitating removal of 2 out of 5 valves.

Conclusions: IBVs are a minimally invasive, well tolerated treatment modality for patients with PAL and a viable alternative to invasive surgical interventions. Procedure or valve-related complications are uncommon. Valves can be removed and do not preclude surgical intervention. Updated guidelines are necessary to formalize PAL management.

Keywords: Persistent air leak (PAL); endobronchial valves; airway valves; bronchoscopy; pneumothorax

Submitted Jun 14, 2022. Accepted for publication Oct 21, 2022.
doi: 10.21037/jtd-22-824
View this article at: https://dx.doi.org/10.21037/jtd-22-824

^ ORCID: 0000-0002-8001-4191.

Introduction

Persistent air leak (PAL) is a challenging clinical problem associated with prolonged hospital stay and increased morbidity (1,2). An air leak is defined as the flow of air into the pleural space. It can occur through a pathologic fistulous tract between a subsegmental or more peripheral portion of the bronchial tree and the pleural space, in which case it is called an alveolar-pleural fistula (APF). It is termed a bronchopleural fistula (BPF) when it occurs between the segmental bronchus or more central airways and the pleural space.

Most air leaks resolve spontaneously with an intrapleural catheter and conservative management, but occasionally air leaks persist (1). PAL is usually defined as an air leak into the pleural space for more than 5 days without a forced exhalation maneuver (1,3). The most common etiologies include pulmonary malignancy, advanced emphysema, cavitary pulmonary infections, acute respiratory distress syndrome, mechanical ventilation, trauma, thoracic surgery, bronchoscopic or transthoracic lung biopsy, and radiofrequency ablation of malignancies (3,4). PAL frequently requires treatment with alternate treatment modalities in addition to conservative management and waiting for secondary healing of the fistulous tract. Historically, these options were limited to intrapleural catheter drainage, surgical repair with video-assisted thoracoscopic surgery (VATS), thoracotomy, or robotic approaches, or mechanical (brushing the pleural surface) or chemical pleurodesis (doxycycline and talc).

The management algorithm for patients with PAL in whom surgical intervention is contraindicated because of comorbidities fails to reflect recent technological advances in the field. The American College of Chest Physicians 2001 consensus statement recommended surgical intervention with VATS if the air leak persists for more than 4 days, and it recommended chemical or mechanical pleurodesis in non-surgical candidates (5). Similarly, the British Thoracic Society 2010 pleural disease guideline recommended surgical consultation if the air leak persists beyond 48 hours (6). Mechanical or chemical pleurodesis is recommended in complex patients who are high risk for surgery as evidence supports efficiency and safety of this approach (6-8). Similarly, autologous blood patch pleurodesis has been shown to be highly effective with a greater than 90% success rate in meta-analyses (9).

As an alternative to surgical intervention or pleurodesis, numerous bronchoscopic techniques have been developed. These options include both sealants (fibrin glue with or without spongy calf bone, histoacryl, oxidized regenerated cellulose, and synthetic hydrogel) and sclerosants (ethanolamine, ethanol, and tetracycline) with variable degrees of success reported (10-19). The endobronchial Watanabe spigot is a silicone implantable bronchial filler that was developed in Japan to treat PAL, but it has lacked general use and adoption internationally (20).

Bronchoscopic placement of removable intrabronchial valves (IBVs) to occlude airways in patients who are not suitable surgical candidates is another well described alternative (21,22). In October 2008, the United Stated Food and Drug Administration approved the Spiration® Valve System (SVS) (Olympus, Japan) for PAL after anatomical surgical resection for pulmonary malignancies. Retrospective case series support IBVs as a safe and effective intervention for PAL after surgical lung resection (23,24). However, many IBVs are placed off-label following pneumothoraces, pulmonary infections, trauma, and malignancies (3). We report our experience with IBVs in the management of PAL for both on- and off-label indications with an evaluation of the time to chest tube removal without the need for another procedure or surgery as our primary endpoint. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-824/rc).

Methods

We performed a retrospective review of our single-center IBV experience from June 2019 to March 2021. The SVS, which carries a humanitarian use device exemption to manage PAL following surgical lung resection, was utilized in all cases. We categorized patients into on-label (any patient with PAL post-thoracic surgery) and off-label (any patient with PAL from all other indications, including infection, pneumothorax, trauma, or post-procedure such as percutaneous or bronchoscopic biopsy) cohorts. For off label indications, IBVs were selected based on consensus after a multidisciplinary discussion with pulmonology, thoracic surgery, trauma surgery, cardiothoracic anesthesia, and hospital medicine teams.

Data collected included demographics, primary pathology leading to PAL, comorbidities, chest tube duration before and after valve placement, number of valves inserted, location of valves, resolution of air leak at the end of the procedure, time to removal of valves, complications, mortality, and need for any additional procedure for PAL

control. Procedure success was defined as chest tube removal without the need for another procedure or surgery and was the primary outcome. Time to chest tube removal after valve placement was used as a surrogate marker for overall resolution of air leak. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institution review board of the Medical College of Wisconsin (IRB# PRO00014839) and individual consent for this retrospective analysis was waived.

Valve placement

Two board certified interventional pulmonologists (JSK, BSB) performed the procedures at our institution in a dedicated bronchoscopy suite or operating room. All patients were intubated, and procedures were performed under general anesthesia, for which the patients were thoroughly evaluated by the cardiac anesthesiology service. General anesthesia was used given the critical illness of many of the patients and the need to ensure accurate monitoring at all times during the procedure for maximum patient safety. Sequential balloon occlusion using a 13-mm balloon (Olympus America Inc., Center Valley, PA, USA) inserted through the working channel of a flexible bronchoscope (Olympus BFTH-190, Olympus America) was used to identify the culprit airway(s). Airway sizing was performed in standard fashion according to the manufacturer's instructions for use using a carefully calibrated 11-mm balloon (Olympus America Inc., Center Valley, PA, USA). Valves were then deployed under direct visualization during a breath hold maneuver.

Post IBV procedure, chest tube management was guided by the primary medical team, which varied between interventional pulmonology, thoracic surgery, trauma surgery, hospital medicine, or providers at referring institutions once patients were deemed safe for return transfer. All patients underwent initial chest tube management with wall suction, ranging from –10 to –40 cmH_2O, followed by clamping trials for at least 24 but no more than 72 hours before chest tube removal. The decision for chest tube removal was also guided by the above primary medical teams with input from the interventional pulmonology team.

Statistical analysis

Descriptive statistics, including mean, standard deviation, range, and percentage, were utilized to describe patient demographics and outcomes. The Mann-Whitney test was used for comparing means using SPSS statistical software (IBM® SPSS® Software version 22.0).

Results

During the study period, 15 patients underwent IBV insertion for PAL. The mean age was 55±17 years with 4 (26.7%) females. A proportion of 66.7% (10/15) of patients were Caucasian (*Table 1*). The on-label cohort contained three patients who developed PAL following thoracic surgery, one each after a total lobectomy, a segmentectomy, or a wedge resection, with two of these patients presenting as transfers from another facility after numerous attempts at water seal and/or clamping trials. The off-label cohort had 12 patients. Six had empyema, four had secondary spontaneous pneumothorax, one had penetrating trauma, and one presented following percutaneous lung nodule biopsy. Numerous comorbidities were seen in our patients, with the majority having underlying pulmonary disease. The mean preprocedural American Society of Anesthesiologists (ASA) score was 3.3±0.5.

An average of 4±0.4 IBVs were placed (*Table 2*). One patient developed progressive hypoxic respiratory failure shortly after insertion of valves, necessitating removal of 2 out of 5 valves. This patient had bilateral PALs secondary to penetrating trauma and was deemed not to be a surgical candidate at the time of IBV evaluation per multidisciplinary discussion.

Before IBV placement, the mean chest tube dwell time was 19±11 days with 12 patients on wall suction (range of –10 to –20 cmH_2O) and one patient on water seal with evidence of PAL on clamp trial (data unavailable for two patients, Table S1). In the on-label cohort (n=3), all subjects had successful removal of the chest tube after a mean duration of 4.0±1.0 days. In the off-label cohort (n=12), 83.3% (10/12) of patients had successful chest tube removal 16.2±5.7 days (P=0.396) after IBV insertion, for a total cohort success of 86.7% (13/15). One patient in the off-label cohort opted for hospice care and was discharged with a chest tube in place. In the second patient, who had bilateral PALs secondary to penetrating trauma, the chest tube was not successfully removed post IBV placement, leading to thoracotomy and wedge resection for definitive management. There was no significant difference between these cohorts. In 13 patients, the chest tube was successfully removed with the mean time of 4.0±1.0 days in the on-label

Table 1 Baseline characteristics of patients receiving intrabronchial valves for persistent air leak

Demographics	Values, n (%)
Age, years (mean ± SD)	55±17
BMI (mean ± SD)	22.34±3.14
Sex	
Male	11 (73.3)
Female	4 (26.7)
Race	
Caucasian	10 (66.7)
African American	5 (33.3)
Smoking	
Former smoker	11 (73.3)
Current smoker	2 (13.3)
Non-smoker	2 (13.3)
Pack year (mean ± SD)	28±18
Primary pathology responsible for air leaks	
Necrotizing pulmonary infections	6 (40.0)
Secondary spontaneous pneumothorax	4 (26.7)
Post-thoracic surgery	3 (20.0)
Trauma	1 (6.7)
Iatrogenic	1 (6.7)
Comorbidities	
Chronic obstructive pulmonary disease	7 (46.7)
Hypertension	7 (46.7)
Primary pulmonary malignancy	5 (33.3)
Coronary artery disease	3 (20.0)
Congestive heart failure	3 (20.0)
Asthma	1 (6.7)
Other pulmonary diseases*	11 (73.3)
Charlson Comorbidity Index	3.6±2.6
ASA score	3.3±0.5

*, other pulmonary diseases include chronic respiratory failure [6], interstitial lung disease [1], bronchiectasis [1], bronchiolitis [1], idiopathic fibrosing pleuritis [1], hypersensitivity pneumonitis [1]. SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologist.

cohort and 13.3±4.6 days in off-label cohort (P=0.396).

After IBV placement, immediate air-leak cessation occurred in five patients, diminished air leak occurred in six patients, and no change occurred in the air leak in four patients, respectively, based on visual assessment of the chest tube management system. In the cohort with immediate air-leak cessation, the average duration of chest tube removal was 12.2 days compared with 15.4 days in the rest of the cohort (P=0.339). Twelve patients had valves retrieved without any complications. In one patient, IBVs were placed as destination therapy because of the low probability of fistula healing in the setting of advanced lung cancer. One patient died secondary to infective endocarditis in the background of intravenous drug use. One patient, whose bilateral PALs were due to penetrating trauma, ultimately required thoracotomy and wedge resection for repair of the PALs. There were no peri or post-procedure related deaths.

Discussion

The primary diagnoses that place patients at higher risk for PAL also make management more challenging as invasive surgical interventions are frequently precluded. Our patients were all at high risk for perioperative mortality based on an average ASA score of 3.3±0.5. Despite the severity of their illness, IBVs were generally well tolerated. In our single center case series using SVS for treatment of PALs, we demonstrate that IBVs are safe and effective for PALs due to both on- and off-label indications, further supporting their value in treating PALs of various etiologies.

In addition to case reports, IBV efficacy for PAL is supported by larger, retrospective case series. The first large case series published in 2009 included 40 patients who received the Zephyr® endobronchial valve (Pulmonx Corporation, CA, USA) (22). The mean duration of air leak from valve insertion to chest tube removal was 21 days (median: 7.5 days). One to nine endobronchial valves were placed per patient with a mean of 2.9±1.9 valves, leading to complete resolution or reduction of air leak in 92.5% of patients. The first case series looking at SVS included eight valve placement procedures with PAL after a median chest tube duration of 4 weeks (range, 18–150 days) before IBV treatment (23). The median and mean duration of air leak after the procedure was 1 and 4.5 days respectively,

Table 2 Outcomes of intrabronchial valve use in the on-label and the off-label cohorts

Underlying etiology of persistent air leak	On-label use	Off-label use					Total	P value
	Post-thoracic surgery	Secondary spontaneous pneumothorax	Necrotizing pulmonary infections	Trauma	Iatrogenic (post-TTNA biopsy)	Total off-label use		
Number of patients	3	4	6	1	1	12	15	
Chest tube dwell time before IBV placement, days (mean ± SD)	19±9	14±12	26±12	21	17	19±12	19±11	0.717
Number of IBV placed per patient (mean ± SD)	3±2.5	5±2	5±1.5	5	3	5±1.6	4±1.8	0.265
Location of IBV placement (n)[1]								NA
Right upper lobe	2	0	2	0	1	3	5	
Right middle lobe	1	0	1	0	0	1	2	
Right lower lobe	1	1	1	0	0	2	3	
Left upper lobe	1	2	4	1	0	7	7	
Left lower lobe	0	1	2	0	0	3	3	
Air leak resolved at procedure end (n)								NA
Resolved	0	2	3	0	0	5	5	
Diminished	1	2	2	1	0	5	6	
Persistent	2	0	1	0	1	2	4	
IBV to chest tube removal, days (mean ± SD)	4.0±1.0	17.5±9.1	15.3±6.3	NA	NA	16.2±5.7	13.3±4.6	0.396
Additional procedures required (n)	0	0	1	1	0	1	2	NA
IBV	0	0	1	0	0	1	1	
Wedge resection	0	0	0	1	0	0	1	
Chemical or mechanical pleurodesis	0	0	0	0	0	0	0	
Days to IBV retrieval (mean ± SD)	79±22	92±49	105±46	NA	NA	99±42	96±41	0.727
Complications (n)								
Immediate respiratory failure	0	0	0	1	0	1	1	

[1], 4 patients had IBV placed in multiple lobes. TTNA, transthoracic needle aspiration; IBV, intrabronchial valve; SD, standard deviation; NA, not applicable.

a median of 3.5 valves was used, and all valves were successful retrieved. There were no procedural or valve-related complications. In a study of 112 patients, 75 patients underwent SVS implantation with a mean of 2.6 vales placed per patient and a median time to air leak resolution of 16 days (24). However, the majority (75%) underwent valve placement for off-label indications. Similarly, IBV may be used as a bridge to lung transplantation to make potential future surgical interventions less difficult (25,26). A large single-center case series of 60 patients reported successful removal of the chest tube in 80% with two patients (3%) having device failure. No deaths were related to the procedure or devices (27). In 2016, Podgaetz *et al.* reported successful chest tube removal 3 days after IBV placement and that this approach was cost effective for PAL expected to last more than 8 days in the Canadian Health Care System (28). In contrast, Hance *et al.* found only a 57% success rate and Ding *et al.* published a meta-analysis showing varied success for complete resolution of PAL, ranging from 48% to 100% (29,30).

Our IBV experience further supports the efficacy and safety described in the literature. Before valve placement, the mean chest tube dwell time was 19±11 days (*Table 2*), which is consistent with prior case series (22,24) and likely reflects our nature as a tertiary academic referral center in which patients were sent to us after numerous attempts at PAL management at their referring institutions. Travaline *et al.* and Gilbert *et al.* described an average time to thoracostomy tube removal of 21 and 16 days, respectively, after IBV placement, which is longer than our average time to removal of 13.3 days (22,24). Travaline *et al.* reported that 15% of patients in their case series experienced adverse events, such as valve expectoration, oxygen desaturation, valve mal-positioning, and pneumonia (22). Only one patient with PAL secondary to trauma and extensive lung injury developed progressive hypoxic respiratory failure shortly after insertion and required valve removal, which is in line with the studies published by Gillespie *et al.* and Bermea *et al.* (23,27).

The mean duration to chest tube removal was 4±1 days in the on-label cohort compared to 16.2±5.7 days in the off-label cohort (P=0.396) (*Table 2*). In the cohort with immediate air-leak cessation after the procedure, the average duration of time before chest tube removal was 12.2 days compared with 15.4 days in the rest of the cohort (P=0.339). These values reflect that not all chest tubes were actively managed by our procedural team. Thus, it is possible that uncontrolled variables, such as reliance on extensive duration of clamping trials per different providers or transfer of patient care to other facilities, may contribute to these findings. The majority of the patients that had immediate air leak cessation developed a recurrent air leak post operatively. Given this finding in our cohort, we elected to be conservative with recommending chest tube removal, which was managed by other primary medical teams besides interventional pulmonology in many cases, to mitigate the risk of recurrence or progression of the PAL leading to tension pneumothorax physiology if the chest tube was removed to early. Although the exact mechanism for this phenomenon is unclear, unmasking of collateral ventilation between lobes is a possible explanation.

Although our study demonstrated 86.7% (13/15) success rate in chest tube removal for all patients with PAL, we acknowledge potential limitations, including its retrospective nature, small sample size, absence of a control group, and the heterogeneity of leak etiologies. The lack of a standardized approach to the chest tube management and chest tube removal by one medical team post-IBV placement might also have prolonged the chest tube dwell time in our cohort. Additionally, it is possible that for the one patient with PAL on water seal and the two patients whose chest tube management plans were unavailable from records review prior to IBV placement that the APF would have eventually healed regardless of IBV therapy if enough time was allowed to elapse. However, we believe that this study contributes meaningful data to the existing body of literature that demonstrates IBVs are a safe and effective less invasive alternative intervention for PALs, even for off-label indications, which may need to be reassessed as data continue to accumulate supporting its efficacy in these patients. Reevaluation of current guidelines for PAL management are likely warranted as this body of literature continues to expand. While randomized controlled trials would ideally overcome many of the limitations from the published literature as well as clarify definitions for successful outcomes, the Spiration Valves Against Standard Therapy (VAST) trial was suspended (31). Until these efforts begin again, it is imperative to continue to acquire and present data that speaks to the safety and efficacy of IBV for treating PAL of various causes in order to advocate for wider acceptance of this technique and better recognition of its value in society guidelines.

Conclusions

IBVs are a minimally invasive, well tolerated treatment modality, and a viable alternative to surgery for patients with PAL. Procedure or valve-related complications are rare. Valves can be removed and do not preclude future surgical intervention. Further evaluation with randomized controlled trials is warranted to determine the optimal timing for IBV insertion in different disease states. Updated guidelines are necessary to standardize the management of this complex disease process and to review potential on and off-label indications.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-824/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-824/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-824/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-824/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institution review board of the Medical College of Wisconsin (IRB# PRO00014839) and individual consent for this retrospective analysis was waived.

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Cite this article as: Singh H, Kurman JS, Jani C, Abdalla M, DePaul B, Benn BS. Off-label use of intrabronchial valves for persistent air leak is safe and effective: a retrospective case analysis. J Thorac Dis 2022;14(12):4725-4732. doi: 10.21037/jtd-22-824