Peer Review File
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Reviewer A

Comment 1. As you recognize, our the JTD aims to be a prestigious, international, leading journal in the world. The detailed indications of EBV (on-label/off-label) may differ considerably between countries and heath care systems. It might be worthwhile to define the on-label/off-label cohort.

We thank the reviewer for this comment. On-label and off label have been more clearly defined in the last paragraph of the introduction. We have added to this paragraph "In October 2008, the United Stated Food and Drug Administration approved the Spiration Valve System for PAL after anatomical surgical resection for pulmonary malignancies."

On-label and off-label has been further clarified in the first paragraph of the method section. We added "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.

Comment 2. Personally, I am very curious on "Conclusions": "EBVs 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 rare. Valves can be removed and do not preclude surgical intervention."
The complications by the EBV would be rare, but unfortunately these are occasionally critical, e.g., migration/airway obstruction, furthermore, these days it is not difficult to apply more advanced devices, which to remedy these fatal problems

I thought that it would be very helpful to the readers/reviewers; the authors must keep instructions for authors. Please, carefully check the draft one more time, especially in the area of references. In my humble opinion, if circumstances allow, the abbreviation should be avoided in the area of "Abstract", furthermore the abbreviation "EBV" has not been defined at the area of "Abstract/Background". Furthermore, I thought that it would be very helpful to the readers if the authors check grammars and typos to improve readability. In several parts in manuscript, it's not easy to understand and to read. To improve readability, it needs to proofread the manuscript.

We appreciate these comments. We have reread the manuscript with close attention for proofreading. Edits and corrections have been made where appropriate to improve

the clarity.

We have also modified the abstract to define the term EBV as endobronchial valves.

Reviewer B

Comment 1. Please clarify that patients with segmentectomy were sub-lobar resections and not wedges.

We have clarified this point as recommended by the reviewer. The on-label cohort had 3 patients and one each had undergone a total lobectomy, wedge resection and segmentectomy. The first paragraph of the results section now states “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.”

Comment 2. I do not agree with the definition of prolonged air leak. In surgical patients, is defined as one that prolongs your hospital stay (usually from the 5th day).

We appreciate the reviewers point and have edited the manuscript as suggested. The second paragraph of the introduction now states “PAL is usually defined as an air leak into the pleural space for more than 5 days without a forced exhalation maneuver.”

Comment 3. When authors talk about surgical repair (open or robotic) please replace them for VATS, thoracotomy or robotic.

This change was made as recommended changes are implemented. The sentence now reads “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)”

Comment 4. I do not understand why for off label indications it was necessary to include a trauma surgeon and not a pulmonologist.

We thank the reviewer for pointing out this omission. Pulmonologists usually lead the multidisciplinary team discussion in our institution and are vital parts of the multidisciplinary team. We have edited the manuscript to reflect this point. The second paragraph of methods now reads “For off label indications, bronchoscopic EBV intervention were selected based on consensus after a multidisciplinary discussion with pulmonologist, thoracic surgery, trauma surgery, and hospital medicine teams.”

Comment 5. I am surprised by the delay to treat the air leak in surgical patients (you say 19 days with chest tube...). Normally in day 5 to 7 you have to solve the problem....

We appreciate the reviewer bringing up this point. These values reflect that these patients presented to us as transfers from another facility (n=2) or as an internal consult (n=1) after numerous failed attempts at chest tube clamping. Once the patients were transferred and evaluated, valves were placed within 2-3 days. This information has been added to the first paragraph of the results.

Comment 6. It seems that in patients whose air leak was resolved with the EBV at the end of the procedure, the chest tube was not removed the next day. Why?

We thank the reviewer for asking for clarification of this point. Our experience showed that while PAL cessation was achieved in some patients immediately post-procedure, many of these same patients would have their PAL resume in the post-operative state. As a result, we elected to be conservative with chest tube removal to mitigate the risk of recurrent/progressive of a pneumothorax. While it is unclear what is the exact physiology of this mechanism, we have postulated that unmasking of collateral ventilation may occur. We have clarified this in the fourth paragraph of the discussion.

Reviewer C

Re: Singh et al., Off label use of endobronchial valves for persistent air leak is safe and effective: A retrospective case analysis. This is a small, single-center, retrospective cohort looking at endobronchial valves as a treatment for persistent air leak. Overall, despite the small sample size, the paper is well-written and cites much (though not all) of the relevant literature; my comments are relatively minor. It will add an additional center's experience to the literature on EBV use as salvage therapy in PAL.

We thank the reviewer for their positive feedback.

Comments:
-Please add a citation after the list of causes of PAL in line 59.

Thank you for the recommendations. We have added two references. Reference 3 is an existing reference, and a new reference (no. 4) is added to the list. PMID:

29268535

-In lines 61 and 67-68, you bring up chemical pleurodesis, which should be expanded somewhat, as there are several different methods, including doxycycline and talc. In addition, blood patching, somewhat controversial though it may be, deserves a mention as well.
We appreciate this point. We have added references to support the use of pleurodesis and expanded this section to include autologous blood patching in the third paragraph of the introduction.

-Line 130: please put the time period for valve retrieval in the text (it is already in your table, but it would be helpful here).

We have added this information in the manuscript as suggested in the third paragraph of the results.

-At least two other cohorts similar in size to your study are not cited, i.e. Hance et al, Annals ATS, 2015 and Podgaetz et al, Canadian Respiratory Journal, 2016. In particular, the former study notes a much lower success rate than your study does, I think it is important to bring up that not all cohorts have demonstrated such a high success rate.

We thank the reviewer for this suggestion and have included both of these references in the second paragraph of the discussion.

-While certainly there are many single case reports of EBVs being used in this circumstance, and surely not all need to be mentioned, you could cite Ding et al, Respiratory Research, 2017, which has a good summary of the pre-2017 case reports and case series.

We thank the reviewer for this suggestion and have included this reference in the second paragraph of the discussion.

-In line 182, you mention RCTs being needed. Such a trial (VAST) was begun but unfortunately has been temporarily suspended.

We have added this information into the limitations paragraph of the discussion.

-While your cohort was largely a older and very sick one, and you allude to this in your conclusion that valves “do not preclude future surgical intervention,” it would be valuable to bring up cases of less severely ill patients in whom valves have been used specifically to make planned future surgical intervention less difficult, such as in patients who will ultimately require lung transplant, e.g. Fischer et al, J Heart Lung Transplant 2012, and Bongers and De Cardenas, J Cystic Fibrosis, 2020.

We appreciate this point and have added both references to the text in the discussion section.

-In line 180, there is “qa” after surgery that should be removed.

This has been removed.

-In line 181, I would make the caveat that complications are relatively uncommon, not rare. The 15% cited in the Travaline, 1/15 in your cohort (6.67%), etc. would suggest complications in the 5-15% range, which I would not consider rare.

This has been changed from rare to uncommon.

Reviewer D

In this paper, the authors reported their experience on the use of EBV to treat PAL in 15 cases from a single centre retrospectively.
The main problems of this paper are:

Comment 1. The total number of cases are small and contain a mix of almost all common etiologies of pneumothorax: post-operative, necrotizing lung infection, secondary spontaneous, traumatic, and iatrogenic.

We agree with the reviewer that our patient populations are heterogenous. We divided them into on-label and off-label use of the EBVs to better provide some context for comparing groups and ascertaining efficacy of the EBV procedure for PAL. We have attempted to clarify this throughout the paper.

Comment 2. The "92.8% success rate" (Line 172) is difficult to comprehend. What are the authors' definition of therapeutic success follow EBV treatment? If cessation of air leak and removal of chest tube happens many days after EBV deployment, could this be interpreted as EBV success?

We appreciate the reviewer’s questioning on this point. Procedure success was defined as chest tube removal without the need for another procedure or surgery and was the primary outcome of the study. We have clarified this throughout the manuscript.

Comment 3. Fifteen patients had EDV deployed. Were there patients intended for EBV deployment, but the airway leading to the leak could not be identified, hence EBV deployment was not done? If yes, how many in the study period?

We appreciate the reviewer asking this question. We did not have any patients during the study period in which the airway leading to the leak could not be identified and EBV was not placed.

Minor comments:
Comment 4. All the cases were done under general anaesthesia. In many other reports, such treatment would be done under local anaesthesia with sedation. Admittedly there are pros and cons for GA and that warrant some discussion.

We appreciate this point and have added in the methods section that all patients were evaluated by cardiac anesthesiology prior to the procedure and a justification for this choice given the need for close monitoring of critically ill patients to maximize patient safety. Moreover, having a patient under general anesthesia will allow for maximal precision in valve deployment.

Comment 5. The patient bilateral traumatic pneumothorax: surgery appear to be the only treatment choice. Trying EBV first needs an explanation.

We have clarified that this patient was recommended for EBV by the trauma and thoracic surgery services given that the patient had bilateral pneumothoraces and multidisciplinary conference agreed that the patient was not a suitable candidate for surgery at the time of presentation for EBV.

Comment 6. The sample size is too small and your simple statistical comparisons did not show any significant difference, as expected. Reporting the statistical comparison and safely be skipped.

We appreciate this point and have provided these values in the interest of full transparency.

Reviewer E

Thank you the authors in summarizing their experience in using one-way valve in treating persistent air leak (PAL). It is good to see more and more patients benefit from this endoscopic treatment option.

We thank the reviewer for this positive feedback.

Comment 1. There are two type of one-way valves available in the market: Endobronchial valve by EBVs (Pulmonx) and the other is intrabronchial valve system of spiration (IBV, Olympus, USA). Some literature has used the term EBV to include

these two systems, while some articles had specified the use of either EBV and IBV respectively.
For clarity, as the authors has used intrabronchial valve system of spiration , I suggest the term “Intrabronchial valve” or “IBV” be used throughout the article.

We appreciate the reviewer’s comment and have made the suggested change to IBV throughout the article.

Comment 2. In the table 2 which show the outcomes of EBV use according to different clinical indications. The author had try to analysis the outcome by grouping patient according to clinical indications. It shows that the number of valve used per patient range from 3 to 5. It probably means that for each patients required a certain number of valves to block all the segmental bronchi of that particular lobe to achieve lobar occlusion to stop air leak. As the total number of patient in this study is fifteen only, I am eager to know the outcome of each patient, and a table listing all the parameters of the 15 patients may allow the reader to interpret the outcome of each patients individually.

We thank the reviewer for this suggestion and have created a Supplementary Table 1 which is patient level data to provide this information.

Comment 3. The chest drain dwell time was 19 +/- 1 days as mentioned in line 123 of the article. Seems this duration is a bit long when compared with the suggestion by international guideline on when to intervene a persistent air leak. The one-way valve is costly and the use of valve would be more cost effective if this is used early as suggested by a recent article (Canadian Respiratory Journal. Intrabronchial Valve Treatment for Prolonged Air Leak:
Can We Justify the Cost? Eitan Podgaetz, Felix Zamora, et al.)

We appreciate this comment by the reviewer and agree that this is a prolonged chest tube dwell time. We believe that this value reflects the nature of our institution as a tertiary referral center in which patients were sent to us after prolonged periods of time at other facilities. We believe that this likely contributed to this increased chest tube time prior to the procedure and have added this to the discussion.

Comment 4. What define success in using one-way valves to treat PAL need further discussion. If time allowed indefinitely, theoretically the leaking point inside the lung will heal and air leak will be stopped and all patient’s chest drain can be taken off. To define as success if a chest drain can be take off after the insertion of IBV no matter the duration is a casual definition of success.

We agree with the reviewer regarding this point that a robust definition of success is challenging. We have clarified our definition of success throughout the paper as “chest tube removal without the need for another procedure or surgery” and have mentioned

that attempts at better defining these outcomes and addressing limitations of case series would ideally be answered by randomized controlled trials, but that unfortunately, the Spiration Valves Against Standard Therapy (VAST) trial, was suspended.

Reviewer F

Overview:
This is a retrospective single-centre case series of 15 patients with persistent air leaks (PAL) treated with endobronchial valves (EBV). The cases are divided into on-label and off-label indications for EBV insertion. Results indicate high rates of PAL resolution after EBV placement in both cohorts. There is a low rate of complications. These results are consistent with other case reports and case series on this topic, some of which are much larger than this case series. It is a well-written manuscript that reasonably states that society guidelines should consider broadening the indications for PAL management with EBVs. There are some points that require clarification as per the comments below:

Comments:
1. Could the authors please explain what this manuscript adds to the current literature currently available on this topic? It is unclear to me what knowledge this manuscript adds beyond the case reports and larger case series already available in the published literature.

We appreciate the reviewers question regarding the additional value that our manuscript adds to the field. We believe that our data further supports the safety and efficacy of IBV treatment for PAL of both on-label and off-label indications. While other data certainly exist, we believe there is a need to continue to add to the canon of information to support this therapy as only the SVS system has received a humanitarian device exemption from the United States Food and Drug Administration. Advocacy is thus needed to gain acceptance for EBV/IBV therapy as part of the management algorithm for PAL. We believe that advocacy will be better informed by the addition of more data. Ideally, this data would be best obtained by randomized controlled trials. Unfortunately, the Spiration Valves Against Standard Therapy (VAST) trial, was suspended. We have added this information into the last paragraph of the discussion for further clarification.

2. Regarding the primary endpoint (time to chest tube removal), the methods do not state how the decision to remove chest tubes was made. Was the decision to remove a chest tube based on a standardized approach? If not, this should be mentioned in the study limitations.

We thank the reviewer for raising this question. Unfortunately, due to the nature of

our institution, we, the interventional pulmonology team, were not always the primary providers responsible for chest tube management. As not all chest tubes were actively managed by our procedural team, 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 our findings. We have clarified this in both the methods and discussion sections.

3. In a similar vein, the authors mention that not all chest tubes were actively managed by their team. The lack of a standardized approach to the management of chest tubes after EBV insertion may have impacted on the primary endpoint, and as such should be mentioned in the study limitations.

We again thank the reviewer for raising this point and have added this information to the methods and discussion sections.

4. Please state whether or not wall suction was used as part of PAL treatment. If it was, duration and pressures used should be reported.

Wall suction was used as part of the PAL treatment strategy. We have added this information to the methods section and provided additional information in a new supplementary table 1 as patient level data.

5. There is a discrepancy between the mean age reported in the results section and the mean age reported in Table 1 that needs to be amended.

Thank you for bringing this our attention. We have corrected it in the manuscript.

6. In the results section describing time to removal of chest tubes (lines 123 to 126), there are two patients in the off-label cohort who do not have chest tube removal, but the reasons for this are only given for one patient. Please add details about the other patient as well. Presumably it's the patient who had 2/5 EBVs removed, but it isn't clear.

We have added additional details into the results section to clarify that this second patient, who had penetrating trauma as the etiology of their PAL, did not have chest tube removal post EBV placement, leading to thoracotomy and wedge resection.

7. There are typos in line 180 and table 2 (chest "tuber" dwell time). In line 60, track should be tract.

We have corrected these in the manuscript.

Reviewer G

This is an interesting retrospective analysis to allow readers to assess the real-life use of intrabronchial valves (Spiration) on and off label use. Overall, I think the manuscript is interesting and has value, although its scope is limited, and may have some factors which was not reported in the study. I have the following comments:

Consider changing EBV to intrabronchial valves (IBV) which are traditionally for Spiration. Endobronchial valve (EBV) typically refers to Zephyr valves.

We appreciate the reviewer's comment and have made the suggested change to IBV throughout the article.

Comment 1. In the patients whom you placed the valves, did all of them show immediate cessation of air leak during the case with balloon occlusion or most of them has slower leak? Did the patients have digital monitoring system to quantify the air leak?

We appreciate this point for clarity regarding the number of patients having immediate cessation of air leak during the case. We have provided this data in the results section and in table 2. "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." These findings mimicked the results of intraoperative balloon occlusion. A digital monitoring system was not available for use.

Comment 2. Regarding PAL in this group of patients, did all of them require suction or were some of them tolerating water seal? Let's say some of them were on water seal, do you then think the fistula were meant to heal anyways… after the prolonged period of time, instead of due to valves placement?

We thank the reviewer for this point. For all the patients in our cohort, persistence of pneumothorax was confirmed while on suction or on water seal with clamping trial. This information has been provided in supplementary table 1 for patient level data. We agree with the reviewer that it is possible that the alveolar-pleural fistula could have healed eventually in patients on water seal, but insertion of endobronchial valves may have facilitated more rapid healing of the pleural defect. Further evaluation of this possibility would require randomized controlled trials, but unfortunately, the Spiration Valves Against Standard Therapy (VAST) trial, was suspended. We added this information into the limitations section of the discussion.

Comment 3. Other potential confounding factors – was all the chest tube sizes the same for all patients? Did any of the patients requiring upsizing chest tube or was this considered? Or, did any patients have more than one chest tube in place? I assume they continue to have some space issue shown on repeat CT chest, which prompts consideration for valves?

We appreciate the reviewer asking for these additional details to allow for more clarity regarding the patient data. This information has been provided as supplementary table 1 for patient level data.