

Peer Review File

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Reviewer A

In the present study, the clinical outcome is assessed and a quantitative CT analysis is performed after bronchoscopic lung volume reduction using 2 different valves in advanced emphysema. The authors conclude that this bronchoscopic lung volume reduction leads to changes in the bronchial walls and leads to clinical improvement. In addition, the authors argue that there is also a difference with respect to the two valves used.

The present work is in itself well structured. However, from my point of view, the following deficiencies are apparent: As already mentioned by the authors, the number of patients included (n=19) is very small. In addition, the two selected groups also show significant differences with respect to lung function. Already stated by the authors stated in their limitations that the outcome might primarily due to the severity of the preceding disease. Both types of valves have the same effect (atelectasis). Since the directly affected bronchi were not evaluated at all, it is also not expected that there could be different effects on the unaffected airways, if the intervention was positive at all. In this respect, a combination of the two subgroups into one main group with maybe a subanalysis is more reasonable.

The present results and data per se actually have nothing to do with the type of valves. Rather, with the effects of the procedure per se. In particular, only the bronchi in the non-involved areas are assessed. Any data on which valve, when is useful is lacking.

Reply 1: We are grateful for the suggestion. We removed the details of comparison about EBV and IBV in the main text, given that these groups have different baseline characteristics and only very small numbers of patients are included in both groups. Part of the comparison were shown in the supplementary tables.

Changes in the text: We have deleted most of results and analysis about comparison of EBV and IBV in the main text as advised (see in Page 8, Line 150-153 and Page 12-13, Line 239-249).

Introduction: In the introduction the authors discuss bronchoscopic lung volume reduction, but it remains unclear why the two valves should have different effects.

Reply 2: Thanks for your advice. This part had been removed from our text as mentioned before.

Material Method: There is a lack of information about the type and distribution of emphysema as well as how fissuring was assessed. It is only mentioned which software was used. An additional illustration of how the measurements were

made using the CT data and a comparison before and after valve insertion would be useful. Overall, it is disturbing that there is no image data before and after the interventions.

Reply 3: We are grateful for the suggestion. Because it was a retrospective study, so the details of screening for patients including type of emphysema and evaluating methods of the fissuring were not specified before due to the word count limit. We have modified in the manuscript as suggested.

Changes in the text: (see Page 5, line 77-80): Inclusion criteria were age over 40 years, nonsmoker status for at least three months, severe airflow obstruction (post-bronchodilator FEV1 <50% of predicted), hyperinflation (total lung capacity (TLC) >100% of predicted and residual volume (RV) >150% of predicted), heterogeneous emphysema (heterogeneity compared to the ipsilateral lobe $\geq 15\%$ difference), and an intact interlobar fissure ($\geq 90\%$ complete). Chartis system was conducted for patients who received EBV therapy during surgery to evaluate the absence of collateral ventilation (CV) (1, 2, 12). And we added an image which showed the airway change before and after the intervention (see Figure 1).

Results: As mentioned earlier, merging the groups would be useful.

Reply 4: Thanks for your advice. We have modified the text as suggested (see in the RESULT section, Page 8-9).

Discussion: the discussion only marginally deals with the different types of valves.

Reply 5: Thanks for your suggestion. As mentioned before, most of the results and analysis details of comparison between EBV and IBV have been removed from the text, so we reduced the related discussion correspondingly. In the future, if possible, we will conduct a multicenter study with larger sample size to further study the two valves.

Changes in the text: We have modified the text: Furthermore, we found that EBV seems to have a more rapid effect on bronchial wall thinning than IBV. This may be partly explained by the study design. The EBV data were obtained from patients in a real hospital setting. These patients seemed to be more severe, with lower FEV1, shorter distance of 6MWD, and higher mMRC scale, even than those reported in most published studies(1, 2, 4, 25). IBV data were obtained from the REACH study, which is a randomized controlled trial. Thus, the baseline parameters in EBV group were worse than those in IBV group. Another noticeable reason is the possible difference in the mechanism between EBV and IBV. However, there was no convincing evidence given that the sample size was too small, and the baseline characters did not match. It is necessary to conduct further head-to-head trials with larger sample size to evaluate whether there are any differences in responses between EBV and IBV (see in Page 12-13, Line 239-249).

Images: pictorial representation of measurements before and after valve placement are missing.

Reply 6: Thanks for your advice.

Changes in the text: we added an image which showed the airway changes before and after the intervention (see Figure 1).

Conclusion:

The work presented here still has significant weaknesses. Overall, the work only shows that with bronchoscopic lung volume reduction there are changes in the airways in the expanded lung segments and an improvement in the clinic.

However, the data do not allow conclusions to be drawn about the nature of the valves and their effects on the bronchial system per se. In this respect, the title and purpose of the study are misleading.

Reply 7: Thanks for your advice. We had deleted this misleading description about the different valves in the title, introduction, and conclusion. Thanks again for your rigorous and helpful suggestion.

Changes in the text: we removed the different valves in the title and introduction.

Reviewer B

The authors present a retrospective study which investigates the changes in QCT derived airway parameters after BLVR. The authors have found that 3 and 4th generation bronchial walls are thinner after treatment. This is an interesting finding and in my opinion worth publishing. However, I believe this manuscript requires major revision as there are multiple issues that should be addressed before publication.

Major comments

- The authors conclude that thinner 3rd and 4th bronchial walls are thinner and that these findings are consistent with clinical improvement. I think this relationship with clinical improvement cannot be claimed based on the current analysis performed by the authors. Please correlate changes in WT to changes in FEV1, RV, 6MWD and TLVR. Is there a relevant and significant correlation?

Reply 1: Thanks for your suggestion. We did seek advice from statisticians before. They believed that correlation analysis with such a small sample size (1 month: N=14; 12 months: N=11) was meaningless to some extent. We clarified it in the discussion as you suggested.

Changes in the text: We clarified it in the discussion as following: However, further correlation analysis was not conducted given that only less than 15 patients were included in the follow up. (see Page 10-11, Line 201-202).

- Please consider pooling the EBV and IBV patients and omit the head to head comparisons. I would be very careful to draw conclusions given that these groups have to some extent different baseline characteristics and only very small

numbers of patients are included in both groups. An additional benefit of pooling is that it will condense the manuscript, improve readability and will highlight the core message of this manuscript.

Reply 2: We are grateful for the suggestion. We have removed the details of comparison about EBV and IBV in the main text. Part of the comparison were showed in the supplementary tables. In the future, if possible, we will conduct a multicenter study with larger sample size to further study the two valves. Changes in the text: We have deleted most of result and analysis about comparison of EBV and IBV in the main text as advised (see in Page 8, Line 150-153 and Page 12-13, Line 239-249).

- Please elaborate more in the discussion section on the (clinical) significance of the findings of this study, could the current findings change the way BLVR with valves is performed, do the authors think we should routinely assess QCT airway parameters? How does it help us understand the physiological changes after BLVR?

Reply 3: Thanks for your suggestion. The present findings in our study only provided a preliminary basis for airway structure changes after BLVR. There was still insufficient evidence to suggest to assess QCT airway parameters before BLVR. We have modified the discussion section (see in Page 11, Line 202-22).

- How are patients instructed to inhale during the acquisition of the CT scan? Is it possible that we are not necessarily looking at true anatomic changes after BLVR but rather more profound inspiration in patients with reduced hyperinflation after blvr? Please address this issue and potential bias. A possible solution could be to perform spirometer guided CT scans.

Reply 4: Yes, the reason of bronchial changes remained uncertain. It could come from true anatomic changes caused by pleural cavity pressure reduction, inflammation reduction, and profound inspiration, or just from bias. We discussed in the discussion section. It was a retrospective study, so the CT information bias did exist. We clarified it in the limitations section. In the future, prospective studies could be conducted to address this bias by performing spirometer during CT scans.

Changes in the text: We have modified our text as you suggested: All measurement and analysis of quantitative CT were based on normal inspiratory CT, rather end-inspiratory CT guided by spirometer. Given that patients with severe emphysema would present dyspnea in all probability, the degree of emphysema and bronchitis in CT would be underestimate or overestimate (see in Page 13, Line 251-254)

- The authors state: "We believe that this thickness reduction of the 3rd- and 4th-generation airway walls may contribute to the responsiveness of the BLVR therapy", please clarify this statement.

Reply 5: Thanks. It was inappropriate to state that in our study. We modified the

discussion section as suggested (see in Page 10-11, Line 196-222).

Minor comments

- There are multiple language, consistency and grammatical issues with the manuscript that unfortunately dilute the message of this interesting manuscript. I think the manuscript would benefit from critical evaluation by a native English speaker.

Reply 6: Thanks. We have checked and modified the manuscript using Editage Editing Service.

- Please further explain/hypothesize why the airway walls are thinner after BLVR. Is it a mechanical aspect, a decrease in airway inflammation, or a combination of both?

Reply 7: Thanks for your advice. Based on present findings, it remained unclear how airway structure changes after BLVR. We listed several possible reasons (see in Page 11, Line 204-222). More rigorous studies would be needed to provide further insights.

- Please combine table 1 and 2 (or include baseline characteristics in table 2)

Reply 8: Thanks. We combined Table 1 and Table 2 as a new Table 1. The comparison materials for EBV and IBV were showed in the Supplementary Tables.

- In table 3 and S1 provide the baseline QCT derived airway parameters (not only the delta)

Reply 9: These two tables would be too huge if all baseline airways were included. We added a new Table 2 titled with "Baseline Ipsilateral and Contralateral Airway Structures" to show the baseline airway parameters.

- The authors consider a TLVR of 350ml as clinically relevant, this MID is debated by both Gompelmann (IJCOPD 2017) and Welling et al. (Respirology 2018).

Reply 10: Thanks for your advice. We have searched the related literatures and realized that the cut-off value of TLVR maybe should be higher. And we added these literatures into the References.

Changes in the text: BLVR can cause target lobe volume reduction (TLVR) (9, 10), and a TLVR of 350 mL measured by quantitative high-resolution CT (HRCT) analysis is assumed to be clinically significant (11). Even though recent studies showed the cut-off value for TLVR should be higher (12, 13) (see in Page 4, Line 54-55).

Reviewer C

The authors present here a study on the tomodensitometric evolution of the structure of the airways after endoscopic pneumoreduction by valve.

This is a retrospective study on a small series of patients (19) treated by two similar techniques but who do not have exactly the same mechanism of action (IBV valves more likely function like umbrellas) and who do not have the same level of proof either.

The problem well explained is that of a response variability that is sometimes significant despite well-established selection criteria, in particular the absence of collateral ventilation. There is therefore a significant need for improvement in this area. The authors therefore propose to describe the modifications of the bronchial structures after BLVR before confirming or not that these modifications are correlated with the clinical course.

This work is interesting and the results in terms of efficacy are consistent with other published trials. However, some results are ambiguous and almost 33% of 12-month data is missing in a very small population.

From y point of vue, these results should be published in a "shortcom" format. To investigate the proposed research question, I strongly encourage the authors to focus on EBV and try to obtain data on a larger population. It could also be interesting to assess whether the initial bronchial anatomy could be related to the clinical evolution of patients after treatments (tolerance, efficacy)

Reply: Thanks for your suggestion. In the future, if possible, we will conduct a multicenter study with larger sample size to further study it.

Reviewer D

Great paper with interesting findings. Generally well written. Only a few small critiques.

1. The last paragraph of the intro is written as if you have yet to perform the study, almost as an IRB or grant proposal ie the retrospective study is complete. The grammar and structure is confusing in this respect.

Reply 1: Thanks for your advice. We have modified our text as you suggested.

Changes in the text: The last paragraph was modified as: The objective of the present study was to detect the bronchial changes after BLVR and find the relationship between these changes and clinical benefits (see Page 4, Line 67-68).

2. In the intro, you mention interest in looking at structural changes but don't given any clinical reasoning. You picked outcome parameters so give use your hypothesis, ie why do you think airway size and wall thickness will change and how does it benefit the patient.

Reply 2: We have observed 4 patients treated with BLVR experiencing intraluminal area (LA) enlargement and percentage of wall area (WA%) attenuation in the non-target bronchi, thus we assumed that airway structures would change after BLVR.

Changes in the text: We have observed several patients treated with BLVR experiencing intraluminal area (LA) enlargement and percentage of wall area (WA%) attenuation in the non-target bronchi(14). Therefore, we hypothesized that the airway structures changed after BLVR, and these changes may contribute to clinical benefits. (See Page 4, Line 63-66).

3. Lastly, in the discussion, you define MCID by FEV1 and 6MWD. This is of course reasonable but there is a lot of data to suggest that even when these values don't meet threshold, patient satisfaction scores and subjective improvement surveys may increase after LVRS or BLVR. Worth discussing this as it should like be included in future larger studies.

Reply 3: Thanks for your suggestion. We sincerely appreciate your advice. However, the sample size was too small in our study, so further correlation analysis was not conducted according to the suggestion by statisticians. In the future, if possible, we would conduct a multicenter study with larger sample size to conduct correlation analysis with airway parameters and FEV1, TLC, RV, 6MWD, and St. George's Respiratory Questionnaire (SGRQ).

Reviewer E

The authors aimed to evaluate the changes in airway structures after EBV or IBV treatment and if these changes correlate with clinical improvements. They found that especially in the 3rd and 4th generation bronchi the wall thickness and area show changes after treatment. This is an interesting topic and the study is well designed using automated software to analyze the airway dimensions.

Furthermore, the authors aimed to compare the efficacy of EBV and IBV treatment and the changes in lung volumes after treatment. I do have the following remarks regarding the submitted paper:

Overall

1. Overall the paper is well readable, but the quality of English could be improved, especially in the results sections. Also, a typing error is made in line 116 (vvalves instead of valves).

Reply 1: Thanks for your kind advice. We have modified "valves" in line 116 (see in Page 7, Line 121).

Abstract

2. The method and results section of the abstract could be improved to be a better summary of the major aspects of the paper. In the abstract the authors state subgroup analysis of EBV vs IBV in bronchial structure changes after treatment as an aim and also give the results. However, this is not mentioned in the introduction and method section as an aim of this study and the results are only shown in a table in the supplement. Furthermore, the authors state that a subgroup analysis is done based on MCID but they do not mention which MCIDs they have used.

Reply 2: We are grateful for the suggestion. We have modified the Methods and Results section in Abstract (see Page 2, Line 30-33, and Line 36-41).

Introduction

3. Line 51: authors mention that a TLVR of 350 mL is assumed to be clinically significant. However, two newer publications show that a TLVR of -563 mL or -22.4% (Welling et al., Minimal important difference of target lobar volume reduction after endobronchial valve treatment for emphysema) or a TLVR of -890 – -1070 mL (49 – 54%) (Gompelmann et al., The minimal important difference for target lobe volume reduction after endoscopic valve therapy) are better suited.

Reply 3: Thanks for your advice. We have searched the related literatures and realized that the cut-off value of TLVR maybe should be higher. And we added these literatures into the References.

Changes in the text: BLVR can cause target lobe volume reduction (TLVR) (9, 10), and a TLVR of 350 mL measured by quantitative high-resolution CT (HRCT) analysis is assumed to be clinically significant (11). Even though recent studies showed the cut-off value for TLVR should be higher (12, 13) (see in Page 4, Line 54-55).

4. Line 58-59: The authors state that answering the question of airway structure changes after BLVR treatment would help to “determine parameters to predict responsiveness to treatment”. However, this parameter can only be determined after treatment and could therefore never be used as a predictor. It will only help to, as they previously stated, clarify the mechanism of action.

Reply 4: Thanks for your suggestion. we hypothesized that the airway structure changes may contribute to clinical benefits. If it could be proved, then baseline airway parameters may be related to the efficacy and tolerance of BLVR.

However, our report only provided a preliminary basis for this topic.

5. The authors describe “detecting whether a difference exists between EBV and IBV” as a secondary aim. This aim has no real connection to their primary aim of detecting structural airway changes. I would suggest leaving out this part in the paper, because I feel that it doesn't add any relevant new information to the paper and they can focus more on their quantitative CT analysis.

Reply 5: We are grateful for the suggestion. We have removed the details of comparison about EBV and IBV in the main text. Part of the comparison were showed in the supplementary tables. In the future, if possible, we will conduct a multicenter study with larger sample size to further study the two valves.

Changes in the text: We have deleted most of result and analysis about comparison of EBV and IBV in the main text as advised (see in Page 8, Line 150-153 and Page 12-13, Line 239-249).

Materials and methods

6. Line 67-69: It is unclear how the authors selected these 24 patients. Are they randomly selected from all treated patients between 2010 – 2018 or are this all the patients that are treated within this time period.

Reply 6: Yes, all treated patients between 2010 – 2018 were included.

Changes in the text: We have modified our text: A total of all 24 patients with advanced emphysema who underwent BLVR with valves (both Zephyr endobronchial valve (EBV) and the intrabronchial valve (IBV) system) at Peking University First Hospital, Beijing, China, between January 2010 and June 2018 were included in the study (see in Page 5, Line 71-74).

7. The inclusion criteria described are for the treatment and not for this study, since in the results sections the authors exclude some patients. These criteria should be described in the method section.

Reply 7: Thanks so much for your suggestion.

Changes in the text: We have modified our text as suggested: Patients with severe pulmonary hypertension, diffusion capacity less than 20%, or severe comorbidities were excluded from the BLVR. HRCT with consolidations other than the target lobe, pneumothorax, or pleural effusion were excluded (see in Page 5, Line 82-83).

8. Based on the description it is unclear if the authors measured the airway parameters only on one segmental/sub-segmental airway of the lobe or if they averaged the numbers of all segmental/sub-segmental airways

Reply 8: Thanks. All the second-(lobar), third-(segmental), and fourth-(sub-segmental) bronchi were measured, and then the median of the parameters was included in the study.

Changes in the text: We have modified our text as suggested: All the second-(lobar), third-(segmental), and fourth-(sub-segmental) of all airways were evaluated. Five parameters, including wall thickness (WT) and WT% (percentage of wall thickness), luminal area (LA), wall area (WA), and WA% (percentage of wall area) at the midpoint of each level of airways were calculated automatically and then the median of these parameters were used to subsequent analysis (see in Page 6, Line 95-99).

9. Line 94-95: The authors state that the degree of emphysema is defined as the proportion of emphysema below -950 HU. The authors probably mean the percentage of lung tissue that is below -950 HU.

Reply 9: Thanks for your help.

Changes in the text: We have modified our text: The percentage of low attenuation area (LAA%) was used to evaluate the degree of emphysema, which was defined as the proportion below the CT density threshold of -950 Hounsfield units (HU) (see in Page 6, Line 101-103).

10. Line 96-98: The authors state that the change in volume of the ventilation

area was quantified, but in the results section it looks like the volume of the entire lobes is calculated and not only of the ventilation area. What do the authors mean by the volume of the ventilation area?

Reply 10: Thanks. We have modified the text.

Changes in the text: Changes in the volume of all lobes, including the target lobe, non-target ipsilateral lobes, and contralateral lobes, were also quantified (see in Page 6, Line104-105).

Results

11. In table 1 the numbers of the subgroups (EBV/IBV) are not corresponding or missing regarding all valve data. It looks like something went wrong with table formatting.

Reply 11: Thanks for your help. We have removed the comparison of EBV and IBV. And we combined Table 1 and Table2 as one table. Now a NEW Table 1 is tilted with "Clinic Characteristics and outcomes before and after BLVR".

12. As they authors state there is a baseline imbalance between the patients in the EBV and the IBV group. However when they compare the groups (Table 4), they do not correct for this imbalance. Furthermore, in the discussion section they state that EBV leads to a better improvement in 6MWD, but this cannot be stated as long as they do not correct for the imbalance at baseline. Furthermore, the EBV group has a remarkably low 6MWD at baseline which raises the question if the 6MWT is executed correctly at baseline, especially because the increase after treatment is so much higher than in other studies. In comparison, a meta-analysis by van Geffen et al. (Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis) included 6 RCTs with EBV and found an overall increase of +49m. The increase in 6MWD is especially notable since the results at 12 month follow-up of the pulmonary function parameters are worse than usually found in other studies.

Reply 12: We are grateful for your suggestion. It was inappropriate to compare the efficacy between EBV and IBV without correcting any imbalance. We have removed the comparison of EBV and IBV.

13. Table 5: the volumes at baseline are different for the different follow-up times. This is probably because the data of some patients is missing. It would be helpful if the authors supply the number of patients per analysis or only include the patients that have data on all timepoints.

Reply 13: Thanks. We have added the number of patients per analysis (see in Table 5).

14. Table 5: At baseline the total volume of the target lobe + the ipsilateral lobe is around 3000 mL. The volume of the contralateral lobes is around 1500 mL. Did the authors only measure the volume of the contralateral lobe or the total volume of all contralateral lobe? I believe it would make more sense to measure the total

volume of the whole contralateral lung than only the contralateral lobe. Furthermore, the authors state in line 152 that the volume of the ipsilateral lobe increases consistent with the reduction in volume of the target lobe, but there is a large difference between the volume reduction of the target lobe and the increase in volume of the ipsilateral lobe.

Reply 14: Thanks for your kind and rigorous help. We corrected the data of contralateral lobe volume (CLV) as the total volume of the whole contralateral lung (see in Table 5). And according to the new results and findings, we modified our text.

Changes in the text: Meanwhile, the volume of ipsilateral lobes increased moderately consistent with them. The contralateral lobes also showed slight amelioration but there was no statistical significance (see in Page 9, Line 172-175).

15. Line 164 – 169: the authors describe a decrease in WT% and WA% in the responder group. However, in both figure 1 and 2, this difference is barely visible due to the large range.

Reply 15: Thanks for your suggestion. The small sample size was an obvious limitation for our study, resulting in the large range shown in the figures. In the future, if possible, we will conduct a study with larger sample size to solve the limitation and reduce bias.

16. Since the authors describe the MCID for TLVR in the introduction, why did they choose to not include this in their responder analysis?

Reply 16: Thanks. We thought if we included TLVR in the responder analysis, the changes of airway would mostly come from pleural cavity pressure reduction. Thus, we only chose FEV1 and 6MWD as criteria for subgroup analysis.

Discussion

17. As they authors state in their limitations: their sample size is small and therefore limits the possibility to draw hard conclusion. For example, the authors state in line 211 that the changes they found in airway parameters are meaningful, but this is still debatable based on the data they present. The presented argument is that wall thickness is significantly reduced in the responder group compared to baseline, but not in the non-responder group. However, this significance is not indicated in table S2 and thus cannot be found in the results presented by the authors.

Reply 17: Thanks for your suggestion. In ipsilateral non-target lobes of responder group, WT% and WA% of 3rd-generation ipsilateral bronchi at 1, 3, and 6 months decreased, WT, WT%, WA, and WA% of 4th-generation bronchi decreased at 1 month. But non-responders showed no consistent bronchial wall changes. The above results were shown in Figure 2-3. But, as you mentioned in the previous question, the range in figures was too large due to the small sample size.

18. Line 245: The authors state that their findings support the perspective that patients with an FEV1 < 15% of predicted should also be considered for valve treatment. However, at baseline their patients have a median FEV1 of 24.5% with an IQR of 18.6 – 29.6% of predicted. Thus only a very small number of their patients had a FEV1 < 15% at baseline, thus this cannot be stated based on their findings.

Reply 18: Thanks for your advice. There were only 2 patients who had a FEV1 < 15% at baseline, so we deleted the state. Thanks again for your help.

19. I would suggest changing the order of paragraphs in the discussion to start with their main aim (change in airway structure) in stead of the change in lobe volume (which is the second aim of this study)

Reply 19: Thanks for your advice. We have changed the order as suggested (see in the Discussion section).