Peer Review File

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Reviewer A

Interesting paper on electromagnetic navigation bronchoscopy focusing on CT-body divergence. The aim of the paper is well described and the study design is clear.
I appreciated the discussion
Reply: Thank you for your recognition of our research.
Changes in the text: None.

Reviewer B

The authors present a thought-provoking approach to overcome CT to body divergence by using a novel lung recruitment strategy with intraprocedural CT Chest after navigation and after biopsy to confirm improvements in the amount of CT to body divergence. As the authors recognize, the sample size (n=10) is quite small. The work would be improved by addressing the following.

Comment 1: "Additionally, we implement a new ventilation strategy that helps maintain the pulmonary region in a static and inflation state during ENB. This strategy eliminates atelectasis..." - while this statement is true while the ventilation circuit is closed, once the circuit is opened to insert the bronchoscope, the lung is no longer in a static state as rapid decruitment of alveoli can occur and atelectasis develops. I would delete or at least change this sentence to reflect this point.
Reply 1: We inserted the bronchoscope through the small hole in the center of the rubber cover above the L-shaped connecting tube (seeing in the following picture) as quickly as possible, which can minimize gas leakage. At the same time, we switch to auto mode through the APL valve and provide a set constant pressure. In this state, the anesthesia machine will slowly deliver air to ensure the set pressure is maintained inside the tracheal intubation. And the pressure during intraoperative CT scanning was consistent with that during the ENB operation. These methods are used to maintain the lungs in a static and inflation state during the placement of a bronchoscope. And our postoperative CT scan can also confirm that the lungs were still in the same state during ENB operation.

Changes in the text: None.

Comment 2: "The study included patients with pulmonary nodules who required peripheral
bronchoscopy with ENB and rapid on-site evaluation (ROSE) between May 1st to August 30th." - please provide the year. Also, can you explain the short interval of time for the inclusion period?

Reply 2: We are sorry for not indicating the year, and we added the year in manuscript (see section Methods-Study setting and subjects, Page 6, line 141-143). This study was approved by the Ethics Committee of our center in April 12, 2023 (approval number: 2023028). In fact, these ten patients were the first ten continue patients who undergo ICNVA-ENB, and the result was satisfied. So, we want to show the result the preliminary results of our research to readers. More result of this study will be obtained when our study completed, and we will present it in future article.

Changes in the text: The study included patients with pulmonary nodules who required peripheral bronchoscopy with ENB and rapid on-site evaluation (ROSE) between May 1, 2023 to August 30, 2023. (Page 6, line 141-143)

Comment 3: "In our early cases, we followed the LNVP strategy and found that patients were prone to intraoperative bleeding and hypotension and decreased oxygenation index" - are these cases included here or does refer to other work/patients? Please clarify

Reply 3: These patients are not included in this study. We firstly tried to improve the accuracy by referring to Lung Navigation Ventilation Protocol (LNVP) of Pritchett MA (References 4, 5), but the result was unsatisfied. Therefore, we changed the ventilation protocol and showed the result in this article. We have described our ICNVA ventilation

strategy in this study (see section Methods- Operating procedures, Page 6-8, line 156-184).
Changes in the text: None.

Comment 4: Limitations/Discussion - as the authors mentioned, this is a small study of 10 patients. I think more information needs to be provided to frame this novel approach in terms of general lung nodules/peripheral pulmonary lesions. It would be helpful to postulate on what patients/nodule characteristics would be best suited for this approach and what may not need this - ie size, location, GGO vs solid. Please provide.
Reply 4: Thanks for your advice. As you know, this article is about the feasibility of ICNVA strategy. As for your concern, we will confirm the advantages, indications, complication and other things in our ongoing prospective cohort study. However, in brief, the types of lesions in this study included bilateral pulmonary nodules, pGGO, mGGO (see Table1) and All lesions were located in the outer third of the pulmonary region, none of them were visible endobronchially (see section Result, Page 9, line 228-230). Currently, it remains unclear which type of pulmonary nodule is more suitable for undergoing ICNVA-ENB, and further large-scale prospective studies are needed to explore this. However, based on early experience at our center, it is speculated that pulmonary nodules in the lower lobes, especially those near the diaphragm with significant CT human errors, may potentially benefit from ICNVA-ENB due to its mechanism-based reduction of CT human errors. It is important to note that this is only a hypothesis and there is currently insufficient evidence to include it in the article.
Changes in the text: None.

Comment 5: I would also mention the lack of access/limited access to O-arms that would make this approach less widely available. Can you recommend alternative methods to make this a more widely used protocol?
Reply 5: This is what we are doing in our ongoing prospective cohort study. We plan to collect a large amount of CT data under ICNVA strategy, and develop a software based on AI algorithms that can automatically output virtual CT data after general anesthesia and bronchoscope implantation by inputting preoperative CT data of patients into this software. Through this software, this technology can be achieved even in the center without an O-arm CT. But currently, intraoperative O-arm CT appears to be indispensable.
Changes in the text: None.

Comment 6: Final point in the discussion - can the authors clarify what of the two parts of the their approach - the ventilation strategy or the CT scan - allowed for the success in terms of localization/ROSE and decrease in CT to body divergence by measurement? I realize it may be hard to say definitively, but both methods have been used separately in other publications. It will be helpful for the reader to get this sense from the authors
Reply 6: As you said that clarifying our approach - the ventilation strategy or the CT scan – allowing the improvement of ENB accuracy by decreasing CT to body divergence is important to readers. In fact, our modified ventilation strategy minimized

atelectasis and the using of CT data after bronchoscope placement under anesthesia for the navigation path planning reduced CT data mismatch. Based on these two points, our method has greatly improved ENB accuracy.

We have described these two points in section Disscusion (Page 12, line 286-300). We also added two sentences to help readers better understand this point (see section Discussion, Paragraph 7, Page 12, line 306-310).

Changes in the text: We believe that this is mainly due to the optimization of ventilation strategy and using of intraoperative CT data under general anesthesia intubation and placement of bronchoscopy for ENB path planning. ICNVA-ENB reduces CT to body divergence from a mechanistic perspective, which can effectively improve the accuracy of ENB. (Page 12, line 301-304)

Comment 7: Radiation dose - additional CT scans are required in this approach, which raises the question of additional side effects. What was the radiation dose - mGy/mSV or DAP for patients undergoing this approach? Please quantify/qualify this in terms of other techniques - cone beam CT, mobile 3D C-arm, traditional 2D C-arm.

Reply 7: Thanks for your reminding. We have added the Radiation dose in our article (see Table 2).

Changes in the text:

Table 2 ENB data of patients

NO.	Probe-lesion distance (mm)	Traditional ENB atelectasis CT-body divergence (mm)	ICNVA-ENB atelectasis CT-body divergence (mm)	ENB operation time(min)	ROSE	Postoperative pathological diagnosis	Radiation dose (mSV)	Complication
1	10	8	5	26	malignant	MIA	6.37	none
2	6	7	6	23	malignant	MIA	5.17	none
3	4	12	10	22	malignant	AAH	3.99	none
4	7	15	12	40	malignant	AIS	4.77	none
5	6	13	6	26	malignant	MIA	6.26	none
6	4	17	7	53	malignant	AIS	3.64	intrapulmonary hemorrhage
7	6	15	7	32	malignant	AIS	4.77	none
9	5	16	5	20	malignant	MIA	4.38	none
9	6	8	4	28	malignant	MIA	7.20	none

10	5	10	4	23	malignant	AIS	4.23	none

NO., number; ENB, electromagnetic navigation bronchoscopy; CT, computed tomography; ICVNA, intraprocedural CT guided navigation with ventilatory strategy for atelectasis; ROSE, rapid on-site evaluation; AAH, adenomatous atypical hyperplasia; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma; MSV, millisievert.

Comment 8: Navigation system used - from the picture and video, it appears to be superDimension version 7. Please confirm and state clearly in the methods.
Reply 8: We have demonstrated the data of navigation system in the methods (see section Methods- Operating procedures, Page 7, line 183-184).
Changes in the text: None.

Reviewer C

This is a small retrospective study aimed to evaluate the effect of using a strict and dedicated ventilatory protocol to prevent atelectasis and counteract CT-body divergence. As expected and in line with previously published papers on this subject, also using EMN, using this protocol is of added use.

Major comment
In my view, the biggest, and major factor of interest here is that the route navigation was performed on a CBCT obtained under anesthesia with an O-ring mobile CT device. The ventilatory strategy is secondary. This should be reflected in the title, abstract and throughout the manuscript.
With this strategy, that seems to work, the biggest problem of CT-to-body divergence due to active inspiration vs passive tidal breathing during navigation is overcome and by doing so, you have converted the procedure much more to a CBCT based navigation procedure as reported by Pritchett, Verhoeven and Casal.
Especially when using EMN, this step using the O-ring CT for planning has consequences due to the inherent error-margins in EMN tracking technology, especially in parallel bronchi. This will have influenced your navigation success significantly.
Reply 1: I can't agree more with your point. So, we added one sentence in section Abstract to emphasize the characteristics of our method. (see section Abstract-method, Page 3, line 57-59)
Changes in the text: During ICNVA-ENB, intraoperative CT data were used for ENB path planning, and a new ventilation strategy were employed to help maintain the pulmonary region in a static and inflation state which reducing CT to body divergence.

(Page 3, line 57-59)

Ventilation strategy

Please indicate where you follow the VESPA- and where you follow LNVP strategy advocated by Bhadra and where and why you chose to adapt in more detail. In the discussion section you refer to both but not in detail.

Reply 2: Thanks for your reminding. We have added some description on this point to so that readers can better understand the improvement principle of ICNVA-ENB. (see section Discussion, Paragraph 5, Page 11-12, line 275-286)

Changes in the text: We followed the VESPA strategy to choose a large-diameter tracheal intubation and reduce inspiratory oxygen concentration. In terms of PEEP, we did not completely follow the VESPA strategy to set it at 8-10cm H2O, but instead of personalized PEEP level. We referred to the lung recruitment strategy in LNVP. Differently, in order to reduce the impact of lung recruitment on the cardiovascular circulation system, the increment-decrement ventilatory strategy was used for lung recruitment, rather than the method of maintaining a constant high pressure of 40cm H2O for 40 seconds in the LNVP strategy. Moreover, in the PEEP level setting, the setting of 10-15cm H2O for upper and middle lobe nodules and 15-20cm H2O for lower lobe nodules in LNVP were abandoned. Because this level of PEEP was found too high and can easily affect the cardiovascular circulation system, leading to hypotension. Therefore, a PEEP of 6-8cm H2O for the upper and middle lobe nodules was set. For lower lobe nodules, PEEP was usually set at 10-12cm H2O. (Page 11-12, line 275-286)

Minor comments:

In the highlight section: please add in the "what is known section" that prior studies on ventilation and anesthesia protocols have shown its value, as stated in your introduction. The discussion on which protocol is better is less relevant in my view.

Reply 3: Thanks for your reminding. Now, we added the description about this point. (see section highlight, Page 4, line 86-89.)

Changes in the text: Prior studies on ventilation protocols, like ventilatory strategy to prevent atelectasis (VESPA) and lung navigation ventilation protocol (LNVP), showed accuracy improvement, but limitedly. (Page 4, line 87-89)

Reviewer D

Thank you for the opportunity to review "Intraprocedural CT guided Navigation with Ventilatory Strategy for Atelectasis (ICNVA): a modified electromagnetic navigation bronchoscopy." This retrospective, observational study of 10 patients with peripheral lung lesions evaluated the effectiveness of ICNVA protocol on reducing CT-body divergence.

This is a well-done study (albeit small) evaluating a solution for the problematic issue of CT-body divergence with exciting results. By using intraoperative CT and a ventilation protocol, the authors demonstrated reduced CT-body divergence compared with pre-op CT – which could be very useful when performing ENB.

Comment 1. Can the authors comment on how much radiation was used when performing the repeated CT scans? Was standard fluoro used during the procedure?
Reply 1: Thanks for your reminding. We have added the Radiation dose in our article (see table 2). And there is no standard fluoro used during the procedure.
Changes in the text:

Table 2 ENB data of patients

NO.	Probe-lesion distance (mm)	Traditional ENB atelectasis CT-body divergence (mm)	ICNVA-ENB atelectasis CT-body divergence (mm)	ENB operation time(min)	ROSE	Postoperative pathological diagnosis	Radiation dose (mSV)	Complication
1	10	8	5	26	malignant	MIA	6.37	none
2	6	7	6	23	malignant	MIA	5.17	none
3	4	12	10	22	malignant	AAH	3.99	none
4	7	15	12	40	malignant	AIS	4.77	none
5	6	13	6	26	malignant	MIA	6.26	none
6	4	17	7	53	malignant	AIS	3.64	intrapulmonary hemorrhage
7	6	15	7	32	malignant	AIS	4.77	none
9	5	16	5	20	malignant	MIA	4.38	none
9	6	8	4	28	malignant	MIA	7.20	none
10	5	10	4	23	malignant	AIS	4.23	none

NO., number; ENB, electromagnetic navigation bronchoscopy; CT, computed tomography; ICVNA, intraprocedural CT guided navigation with ventilatory strategy for atelectasis; ROSE, rapid on-site evaluation; AAH, adenomatous atypical hyperplasia; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma;

MSV, millisievert.

2. Could the authors clarify how breath holds were performed during the navigation procedure? Were breath holds performed during biopsy? How long were the breath holds?

Reply 2: We used the APL valve to achieve breath holding, following the LNVP strategy. Setting the APL valve to auto mode and setting a constant pressure. In this mode, the anesthesia machine will maintain the pressure inside the tracheal intubation at the preset pressure level. After holding breathing for 7 seconds, we started CT scanning and biopsy operations. And maintaining breath holding during the biopsy operation. Now, we have added the description about this point. (see section Method-Operating procedures, Page 7-8, line 173-181, 194)

Changes in the text: 5) Patients were maintained at the end of inspiratory state to minimize lung movement during breathing by using adjustable pressure limiting (APL). The APL valve (also referred to as an expiratory valve, relief valve or spill valve) is a type of flow control valve that will ensure the circuit will maintain airway pressure during breath-holding maneuvers (5). Manually APL valve was used at the end of inspiration to maintain the PEEP at desired level (airway pressure≤35cmH2O), following a protective lung ventilation strategy. After setting the APL valve to auto mode and setting a constant pressure, the anesthesia machine would maintain the pressure inside the tracheal intubation at the preset pressure level.

6) After holding breathing for 7 seconds, CT scan (O-arm CT, Siemens Somatom Confidence 64 sliding gantry, Siemens Healthcare) was performed with a layer of 1mm thickness.

Following the CT scan, we utilized ROSE in all cases when they were kept in breath hold state. (Page 7-8, line 173-181, 194)

3. Could the authors clarify how much time after lung recruitment/vent protocol implementation and post intubation CT was performed that the ENB took place? Could the authors comment on the wide range of ENB operation time and how that may have affected the results?

Reply 3: We performed CT scan 7 seconds after lung recruitment/vent protocol implementation, and complete path planning within 5 minutes after obtaining CT data. The ENB operation time usually less than 10 minutes. The entire process, including biopsy procedures was generally completed within 15-30 minutes. We have described the ENB operation time in Table 2 (see following table). As for the results of these 10 patients, we have not observed the operation time having an impact on safety or ENB accuracy. But considering that the current sample size of this study is too small, we are very cautious and cannot determine the effect of operation time. We also hope that as more patients receive ICNVA-ENB, more data can be obtained to determine the impact of operation time.

Changes in the text: none.

Table 2 ENB data of patients

NO.	Probe-lesion distance (mm)	Traditional ENB atelectasis CT-body divergence (mm)	ICNVA-ENB atelectasis CT-body divergence (mm)	ENB operation time(min)	ROSE	Postoperative pathological diagnosis	Radiation dose (mSV)	Complication
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4	7	15	12	40	malignant	AIS	4.77	none
5	6	13	6	26	malignant	MIA	6.26	none
6	4	17	7	53	malignant	AIS	3.64	intrapulmonary hemorrhage
7	6	15	7	32	malignant	AIS	4.77	none
9	5	16	5	20	malignant	MIA	4.38	none
9	6	8	4	28	malignant	MIA	7.20	none
10	5	10	4	23	malignant	AIS	4.23	none

NO., number; ENB, electromagnetic navigation bronchoscopy; CT, computed tomography; ICVNA, intraprocedural CT guided navigation with ventilatory strategy for atelectasis; ROSE, rapid on-site evaluation; AAH, adenomatous atypical hyperplasia; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma; MSV, millisievert.