ANNALS OF PALLIATIVE MEDICINE

Peer Review File

Article Information: http://dx.doi.org/10.21037/apm-20-1029

Review Comments A

Left lateral position to endoscopic submucosal dissection (ESD) may lead to transient impairment of pulmonary function. In this manuscript Wang et al. used electrical impedance tomography (EIT) in 22 patients under general anesthesia for bedside real-time monitoring regional changes in ventilation to assess the changes of regional lung aeration and ventilation in patients undergoing ESD.

This well- written paper about the results of a small clinical trial on a very important issue, regional ventilation and general anesthesia. However, my concern is that the the design and results have little to do with palliative care. Although some patients may actually have cancer, it not well characterized the palliative aspect of the paper. In my opinion, this manuscript is more suitable for anesthesia, intensive care or respiratory journals. I don't think any review would change this. In the way the paper in presented is out of scope of the Annals of Palliative Medicine.

Reply: Thanks for the reviewer's comment that the investigation topic of this paper is rather important. As APM journal official announcement, the aims and scope of APM journal are that "The aim of the journal is to provide up-to-date and cutting-edge information and professional support for health care providers in palliative medicine disciplines to improve the quality of life for patients and their families and caregivers. Annals of Palliative Medicine covers palliative medicine across all multidisciplinary aspects, including oncology, psychology, surgery, nursing, public health, education, nutrition, sociology, ethics, and policy. Furthermore, the journal focuses on cutting-edge developments in the transition from preclinical to clinical research like multimodality therapy, diagnosis, markers, imaging, biology, pathology, prevention, and technical advances related to palliative medicine." (1) In this study, we evaluate the changes of regional lung aeration and ventilation in patients undergoing ESD using electrical impedance tomography (EIT), aiming to reduce pulmonary complications. This study improves the quality of life for patients. (2) Up to now, there is lack of evidence regarding the potential application of EIT on real-time monitoring intraoperative lung ventilation status of patients. Our study

demonstrates that, through EIT imaging, an increasingly implied non-invasive instrument, ESD procedure did not lead to significant changes in either regional ventilation distribution or homogeneity. So, these findings provide cutting-edge information about technical advances, which is consistent with the aim of APM journal. (3) In this study, patients with early gastric cancer and other upper gastrointestinal diseases undergoing elective ESD surgery were enrolled. Therefore, the current manuscript is within the scope of APM journal that covers all multidisciplinary aspects, including oncology and surgery.

Review Comments B

General comments:

The authors evaluated 22 patients with electrical impedance tomography (EIT) to assess the changes in regional lung aeration and ventilation caused by general anesthesia for Endoscopic submucosal dissection in the left lateral position. They found, after tracheal intubation, a decrease in the ventilation of dependent lung (left lung) associated with a reduction in aeration (end-expiratory lung impedance - EELI). After extubation, some changes returned to the level before anesthesia.

I believe that is necessary to add to the manuscript (Introduction and Discussion) some references that discuss the physiology of ventilation in lateral position (both during spontaneous breathing and general anesthesia) and also studies that evaluated ventilation during lateral decubitus using EIT.

Reply: Thanks for this constructive suggestion. We have added the discussion about the physiology of ventilation in lateral position ((both during spontaneous breathing and general anesthesia) in Introduction section and also compared our results with the findings of other studies using EIT during lateral position in Discussion section in revised file (See page 5 line12-23, page 16 line14-17, line 21-22 and page 17 line 13-17).

Changes in the text: Page 5 line 12-23: In spontaneous breathing, the ventilation is greatest in the most dependent lung regions, which is due to the gravity gradient and to the fact that the lower diaphragm, on the dependent side, is able to contract more efficiently (5, 6). This is the known gravity-dependent phenomena that dependent lung regions receive a higher portion of inspired gas in lateral position during spontaneous tidal breathing. However, after induction of general anesthesia, lateral positioning has shown to cause curvature of the diaphragm by abdominal

content and basal parts of the dependent lung may become atelectatic (7). In addition, the lung compliance is decreased and a distinct redistribution of ventilation in favor of the dependent regions is also happened when in lateral decubitus position (8). Traditionally, it has been suggested that gravity is the main physiological determinate that contributes to the non-homogeneous distribution of ventilation in the mechanical lungs (9, 10).

Page 16 line 14-17: While other studies indicate the finding of greater ventilation in the dependent lung in spontaneous breathing (5). This consistency may be due to the effect of placing the electrodes in transverse planes at different thoracic levels.

Page 16 line 21-22: This finding corresponds with previous studies which showed a significant shift of ventilation towards the nondependent lung after being positioned on their side (7).
Page 17 line 13-17: The observed changes in EELI distribution most likely result from the same gravitational factors that contribute to the non-homogeneous aeration distribution in patients with left lateral (9, 10). The results were consistent with previous studies that also suggest the ventilation-related changes in impedance along the craniocaudal axis were in agreement with traditional respiratory physiology (37).

Specific comments:

#1 Title –
Comment: remove the abbreviation "ESD" from the title and try to rephrase the title using the same words, for example: "Lung aeration and ventilation after general anesthesia in left lateral position: a prospective observational study using electrical impedance tomography".
Also, remove the abbreviation "ESD" from the running title.
Reply: Thanks for this suggestion. As advised, we have modified our title and running title, to make them more precise and clear (See page 1, line 1-5).
Changes in the text: Page 1, line 1-5: Title: Lung aeration and ventilation after general anesthesia in left lateral position: a prospective observational study using electrical impedance tomography. Running title: Lung aeration and ventilation measured by electrical impedance tomography with left lateral position.

#2 Abstract – Conclusions, page 3 line 54: "In patients with left lateral position undergoing ESD, left lung was characterized by more de-recruitment .."

Comment: I believe it is better to say a decrease in ventilation because the word "de-recruitment" seems to give the idea that lung collapse has been estimated. The same is also valid for the first paragraph of the Discussion (page 11, line 221).

Reply: We totally agree that it's better to say a decrease in ventilation. Therefore, we have replaced "de-recruitment" with "decreased ventilation" in Abstract and Discussion section (See page 4 line 1-2 and page 15 line 4-5).

Changes in the text: Page 4 line 1-2: In patients with left lateral position undergoing ESD, left lung was characterized by decreased ventilation and more inhomogeneity while right lung was opposite after intubation.

Page 15 line 4-5: After intubation, left lung was characterized by decreased ventilation, as suggested by the lower ventilation proportion.

#3 Abstract – Conclusions, page 3, line 56: "After extubation, regional lung ventilation and homogeneity returned to the level before anesthesia,…"

Comment: You said that the ventilation distribution returns to the values before intubation, but there is a difference between right and left ventilation during surgery and after extubation that did not exist before intubation (figure 2).

Reply: Thanks for this question. We agree with the reviewer that we could not make the conclusion that after extubation, regional lung ventilation returned to the level before anesthesia. Therefore, we have now rewritten this sentence to keep the conclusion rational in the revised manuscript (See page 3 line 21-22 and page 4 line 3-5).

Changes in the text: Page 3 line 21-22: After extubation, the GI values in right and left lung were both returned to the level before anesthesia.

Page 4 line 3-5: ESD procedure with carbon dioxide insufflation did not lead to significant changes in either regional ventilation or homogeneity. And the change of lung inhomogeneity during ESD procedure is transient.

#4 Background, pages 4 and 5

Comment: in the Introduction, it would be interesting to discuss the physiology of the lateral decubitus a little more, both during spontaneous breathing and general anesthesia. There are no references for this topic in the text.

Some studies used EIT to evaluate ventilation distribution in the lateral position, and I believe that they should be included in the Discussion:

1) Šribar A, Merc V, Peršec Z, Peršec J, Milas I, Husedžinović S. Influence of different PEEP levels on electrical impedance tomography findings in

patients under general anesthesia ventilated in the lateral decubitus position. J Clin Monit Comput. 2020;34(2):311-318. doi:10.1007/s10877-019-00318-8
2) Ericsson E, Tesselaar E, Sjöberg F. Effect of Electrode Belt and Body Positions on Regional Pulmonary Ventilation- and Perfusion-Related Impedance Changes Measured by Electric Impedance Tomography. PLoS One. 2016;11(6):e0155913. Published 2016 Jun 2. doi:10.1371/journal.pone.0155913
3) Kao TJ, Amm B, Wang X, et al. Real-time 3D electrical impedance imaging for ventilation and perfusion of the lung in lateral decubitus position. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:1135-1138. doi:10.1109/EMBC.2014.6943795

Reply: We agree with the reviewer's constructive suggestions. We have discussed the physiology of the lateral decubitus both during spontaneous breathing and general anesthesia with cited references in the revised Introduction section. Also, after carefully considering these three references, we have now included them for more systemically discussing the use of EIT in lateral position in the revised Discussion section (See page 5 line12-23, page 16 line14-17, line 21-22 and page 17 line 13-17).

Changes in the text: Page 5 line 12-23: In spontaneous breathing, the ventilation is greatest in the most dependent lung regions, which is due to the gravity gradient and to the fact that the lower diaphragm, on the dependent side, is able to contract more efficiently (5, 6). This is the known gravity-dependent phenomena that dependent lung regions receive a higher portion of inspired gas in lateral position during spontaneous tidal breathing. However, after induction of general anesthesia, lateral positioning has shown to cause curvature of the diaphragm by abdominal content and basal parts of the dependent lung may become atelectatic (7). In addition, the lung compliance is decreased and a distinct redistribution of ventilation in favor of the dependent regions is also happened when in lateral decubitus position (8). Traditionally, it has been suggested that gravity is the main physiological determinate that contributes to the non-homogeneous distribution of ventilation in the mechanical lungs (9, 10).

Page 16 line 14-17: While other studies indicate the finding of greater ventilation in the dependent lung in spontaneous breathing (5). This consistency may be due to the effect of placing the electrodes in transverse planes at different thoracic levels.

Page 16 line 21-22: This finding corresponds with previous studies which showed a significant shift of ventilation towards the nondependent lung after being positioned on

their side (7).

Page 17 line 13-17: The observed changes in EELI distribution most likely result from the same gravitational factors that contribute to the non-homogeneous aeration distribution in patients with left lateral (9, 10). The results were consistent with previous studies that also suggest the ventilation-related changes in impedance along the craniocaudal axis were in agreement with traditional respiratory physiology (37).

#5 Methods, Page 8, line 143: "… (2) EELI variation (Δ EELI), expressed in ml ….."

Comment: Was EELI variation expressed in ml?

Reply: We recorded changes in EELI in arbitrary units (a.u.) as previously reported (*Lars Eichler, Jakob Mueller, Jorn Grensemann, et al. Lung aeration and ventilation after percutaneous tracheotomy measured by electrical impedance tomography in non-hypoxemic critically ill patients: a prospective observational study. Ann. Intensive Care. 2018, 8:110).* Therefore, we have modified this sentence in the revised manuscript (See page 10 line 2).

Changes in the text: Page 10 line 2: (2) EELI variation (Δ EELI), values shown as arbitrary units (a.u.).

#6 Results, Figure 1 (page 23)

Comment: explain in the legend what is "dynamic image" and "tidal image".

Reply: Thanks for this suggestion. We have added the explanation of dynamic image and tidal image in the revised legend (See page 28 line 4-7).

Changes in the text: Page 28 line 4-7: Dynamic image represents the changes in tissue properties between a baseline (reference) measurement frame and the current frame. Tidal image represents the difference of impedance between end-inspiration and end-expiration.

#7 Results, page 9, lines 177 and 180: "… decrease into the baseline after extubation (M1, 50.4% vs M4, 59.4%) "

And

"….increase into the baseline after extubation (M1, 49.6% vs M4, 40.6%)"

Comment: please clarify the meaning of these sentences. Are there significant differences in those results?

Reply: Thanks for this suggestion. There was no significant difference between M1 and M4 in right ventilation proportion or left ventilation proportion. We have rewritten these sentences to make their meaning more clear and more focus (See

page 12 line 7-13).

Changes in the text: Page 12 line 7-13: Comparison of right lung ventilation at the four distinct time points of the procedure showed significant increase after intubation（M1, 50.4% *vs* M2, 63.8%, $p<0.05$）and then returned to the baseline level after extubation (M1, 50.4% *vs* M4, 59.4%, $p>0.05$). While, comparison of left lung ventilation at the four distinct time points of the procedure showed significant decrease after intubation (M1, 49.6% *vs* M2, 36.2%, $p<0.05$) and then returned to the baseline level after extubation (M1, 49.6% *vs* M4, 40.6%, $p>0.05$).

#8 Results, page 10, lines 194-5: "The right and left lung regions showed a significant decrease in volume.."

Comment: Was it a decrease in volume or aeration?

Reply: A fall in EELI may just reflect aeration loss, so it should be a significant decrease in aeration. We have corrected this sentence in revised file (See page 13 line 5-8).

Changes in the text: Page 13 line 5-8: The right and left lung regions showed a significant decrease in aeration compared with the level after surgery and before extubation (Δ EELI right -497 [-960; -101]; left -268 [-2294; 143]) (Table 2).

#9 Results, Table 2 (Page 29)

Comment: it would be better to move the "right" and "left lung" to the columns and explain which are EELI variation measured "after intubation" and "after extubation" in the rows

Reply: Thanks for good suggestion. We have modified Table 2 as above suggested, to make the table more clear (See page 30).

Changes in the text:

Table 2 Changes in EELI

	Right lung	**Left lung**
ΔEELI measured		
After intubation	161 [-952; 1905]	-87 [-809; 253]
ΔEELI measured		
After extubation	-497 [-960; -101]	-268 [-2294; 143]

#10 Results, Page 10, lines 198 -200: " A value close to 0.5 does not necessarily mean a homogeneous …"
Comment: it would be better to move this explanation to the methods section.
Reply: Thanks for the advice. We have moved this explanation to Methods section in revised manuscript (See page 10 line 12-15).
Changes in the text: Page 10 line 12-15: A value close to 0.5 does not necessarily mean a homogeneous air distribution in the whole respiratory system, but a value close to 1 definitely means inhomogeneous distribution between the left and right lungs according to EIT data.

#11 Page12, lines 226-7: "…… and (3) After extubation, regional lung ventilation and homogeneity were back to the level before anesthesia. Taken together, these findings suggest temporary changes of.."
Comment: See comment number #3.
Reply: Thanks for this question. We agree with the reviewer that we could not make the conclusion that after extubation, regional lung ventilation returned to the level before anesthesia. Therefore, we have corrected in Discussion section of revised manuscript (See page 15 line 10-12).
Changes in the text: Page 15 line 10-12: (3) After extubation, regional lung homogeneity was back to the level before anesthesia. Taken together, these findings suggest temporary changes of lung status during the whole ESD surgery.

#12, Discussion, page 12, lines 229-30 "To our knowledge, this is the first report directly describing regional lung ventilation and impedance changes in ESD patients with left lateral position at the bedside."
Comment: I am not sure if this statement is relevant. Consider deleting it.
Reply: Yes, we have deleted this statement in the revised manuscript (See page 15 line 12).

#13 Page 12, lines 237- – "During ESD under general anesthesia in left lateral position, gas exchange is impaired because of a mismatch of the regional distribution of ventilation and perfusion."
Comment: add a reference about lateral position during anesthesia.
Reply: We have added a reference related with lateral position during anesthesia in above mentioned sentence in revised manuscript (See page 15 line 18-20).
Changes in the text: Page 15 line 18-20: During ESD under general anesthesia in left lateral position, gas exchange is impaired because of a mismatch of the regional

distribution of ventilation and perfusion (35).

#14 Discussion

Comment: compare your results with the findings of other studies using EIT during lateral position cited in comment #4

Reply: Thanks for this constructive advice. As the reviewer's advice, we have compared our results with the findings of other studies using EIT during lateral position in revised Discussion section (See page 16 line14-17, line 21-22 and page 17 line 13-17).

Changes in the text: Page 16 line 14-17: While other studies indicate the finding of greater ventilation in the dependent lung in spontaneous breathing (5). This consistency may be due to the effect of placing the electrodes in transverse planes at different thoracic levels.

Page 16 line 21-22: This finding corresponds with previous studies which showed a significant shift of ventilation towards the nondependent lung after being positioned on their side (7).

Page 17 line 13-17: The observed changes in EELI distribution most likely result from the same gravitational factors that contribute to the non-homogeneous aeration distribution in patients with left lateral (9, 10). The results were consistent with previous studies that also suggest the ventilation-related changes in impedance along the craniocaudal axis were in agreement with traditional respiratory physiology (37).

#15 Discussion, page 13, lines 259-264: " This is similar with previous studies which showed formation of left located atelectasis upon induction of anesthesia in left lateral subjects (25)….. anesthesia-induced atelectasis" (26)."

Comment: Did references 25 and 26 evaluate patients in the lateral position?

Reply: We have now carefully assigned references related to the evaluation of patients in the lateral position and compared them with our findings in Discussion (See page 16 line 21-23 and page 17 line 1-3).

Changes in the text: Page 16 line 21-23 and page 17 line 1-3: This finding corresponds with previous studies which found a significant shift of ventilation towards the nondependent lung after being positioned on their side (7). In left lateral position, the ventilation gradient is redistributed along the gravitational axis. The subsequent compression of left lung areas by right abdominal organs may be the most important pathophysiological causes of "left lateral positioning anesthesia-induced atelectasis" (37).

#16 Discussion, page 13, lines 269: "…. ventilation is transit"
Comment: there is a typo in the word "transit".
Reply: We have rewritten this sentence in revised manuscript (See page 17 line 3-5).
Changes in the text: Page 17 line 3-5: Moreover, during surgery, there was not significantly more ventilation in the right lung or less ventilation in the left lung happened, indicating carbon dioxide insufflation during ESD procedure had no significant effect on regional ventilation.

Review Comments C
Comments to the authors:

1. **I am bit sceptical about induction in lateral position when not highly indicated. This is not a safe practice.**

Reply: This is a good question. The safety and effectiveness of endotracheal intubation technique in lateral patient positioning is now successfully established in our team with publications:
Publication 1: *Hui Li, Wu Wang, Ya-Ping Lu, et al. Evaluation of Endotracheal Intubation With a Flexible Fiberoptic Bronchoscope in Lateral Patient Positioning: A Prospective Randomized Controlled Trial. Chin Med J (Engl). 2016 Sep 5;129(17):2045-9.*
We conducted prospective randomized controlled two-center trial and found the median total time to tracheal intubation was significantly lower and hemodynamic changes immediately after intubation were more alleviated in patients with lateral position compared to patients with supine position.
Publication 2: *Yue Jin, Jing Ying, Kai Zhang, et al. Endotracheal Intubation Under Video Laryngoscopic Guidance During Upper Gastrointestinal Endoscopic Surgery in the Left Lateral Position: A Randomized Controlled Trial. Medicine (Baltimore). 2017 Dec;96(52):e9461.*
In this study, we found intubation in the lateral position can prevent the hemodynamic change and sore throat resulting from change in decubitus, suggesting it's safe and feasible to perform intubation under video laryngoscopic guidance in the left lateral position.
Also, there are some other published findings to confirm the safety of induction in lateral position: *Ichiro Takenaka, Kazuyoshi Aoyama. Prevention of Aspiration of Gastric Contents During Attempt in Tracheal Intubation in the Semi-Lateral and Lateral Positions. World J Emerg Med. 2016;7(4):285-289; Komatsu R, Kamata K,*

You J, et al. Airway scope for tracheal intubation in the lateral position. Anesth Analg. 2011 Apr;112(4):868-74.

Therefore, these studies suggest induction in lateral position as a safe practice. The references have been added in the revised manuscript (See page 8 line 11-13). Indeed, we also have rich clinical experience to perform intubation in lateral position.

Changes in the text: Page 8 line 11-13: Before anesthesia induction, patients were placed in left lateral position with a shoulder pad to ensure adequate cervical reclination and to avoid positional changes between measurements (25, 26).

2. **Why fixed tidal volume of 8 mL/kg selected and that too in the era of lung protective ventilation when you yourself assumed that this surgery in lateral position leads to high risk of VILI?**

Reply: An international expert panel-based consensus was reached for 22 recommendations and four statements of lung-protective ventilation for the surgical patients in 2019 (*Christopher C Young, Erica M Harris, Charles Vacchiano, et al. Lung-protective Ventilation for the Surgical Patient: International Expert Panel-Based Consensus Recommendations. Br J Anaesth. 2019 Dec;123(6):898-913*). In this consensus, a tidal volume of 6-8 ml·kg^{-1} predicted body weight, is strongly recommended and a fundamental component of lung-protective ventilation strategy. However, the use of a low tidal volume without adequate PEEP may increase the risk of atelectrauma as a result of cyclic lung de-recruitment (*Yang D, Grant MC, Stone A, et al. A meta- analysis of intraoperative ventilation strategies to prevent pulmonary complications: is low tidal volume alone sufficient to protect healthy lungs? Ann Surg. 2016; 263: 881e7; Cai H, Gong H, Zhang L, et al. Effect of low tidal volume ventilation on atelectasis in patients during general anesthesia: a computed tomographic scan. J Clin Anesth. 2007; 19: 125e9*). We have added these references in Methods section in the revised manuscript (See page 8 line 21-22 and page 9 line 1-2). In this submitted manuscript, we mainly focus on the change of lung ventilation and aeration of patients in lateral position during ESD. And given that ESD procedure accompanied by repetitive carbon dioxide insufflation may contribute to the collapse of the left lung, we choose a ventilation setting of 8 ml·kg^{-1} tidal volume as consensus recommended.

Changes in the text: Page 8 line 21-22 and page 9 line 1-2: Following muscle relaxation, all patients were tracheally intubated and ventilated mechanically using a Primus respirator (Dräger, Lübeck, Germany) in a volume-controlled mode (tidal volume of 8 ml·kg^{-1} of ideal body weight, a standardized PEEP level of 0 cm H_2O and inspiration-to-expiration ratio of 1:2) (28-30).

3. **Why no PEEP was used? This kind of surgery is known to cause rise in intraabdominal pressure and subsequent hindrance to diaphragmatic excursion. I am not convinced.**

Reply: We agree with the reviewer's comment that PEEP applied during the entire ESD procedure may be one important setting to reduce the risk of VILI. However, the optimal level of PEEP remains a matter of debate. One large trial protective ventilation during general anesthesia for open abdominal surgery found that high versus low PEEP showed no difference in the development of postoperative pulmonary complications (*Hemmes SN, Gama de Abreu M, Pelosi P, et al. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014; 384: 495e503*). So, the issue as the referee mentioned above needs further investigation to titrate "best PEEP" according to EIT-derived indices. In this manuscript, we focus exclusively on the effect of ESD operation with carbon dioxide insufflation on lung status in patients with lateral position using EIT apparatus. Therefore, in the current manuscript, we did not include the research about the effect of PEEP during ESD procedures.

4. **To me power of study calculation looks suspicious.**

Reply: Thanks for this reminder. We have rewritten this part, to make them more precise and clear in revised manuscript (See page 10 line 20-22).

Changes in text: An a priori power calculation (G*Power 3.1.9.2, Universities of Kiel and Dusseldorf, Germany) revealed a sample size of 19 to be sufficient to detect a difference in lung ventilation with calculated effect size of 0.28 to achieve an error probability for $\alpha = 0.05$ and $1-\beta = 0.80$.

5. **Changes in ventilation in lateral position well studied and well known. This sophisticated equipment did not reveal different thing. What you actually intended to find here? EIT only evaluated changes in ventilation, but perfusion and matching on V/Q are also important for final gas exchange. Those were not evaluated. Moreover choice of maintenance of anaesthesia can also influence the regional ventilation which has not been highlighted, neither mentioned. Lack of PEEP has huge impact here as is the hypoxic pulmonary vasoconstriction. Without stressing them mere evaluation of ventilation does not have much clinical impact.**

Reply: Thanks for these insightful suggestions. On one hand, we intended to noninvasively and instantaneously evaluate the effect of carbon dioxide insufflation during ESD procedure on regional ventilation and homogeneity using EIT. As we

know, repetitive carbon dioxide insufflation may increase the risk for respiratory function impairment and lead to postoperative pulmonary complications thereafter. In our study, using EIT monitoring, we found that ESD procedure with carbon dioxide insufflation did not lead to significant changes in either regional ventilation distribution or homogeneity which is not previously reported. More importantly, we also found that after extubation, regional lung homogeneity was back to the level before anesthesia, suggesting the change of lung inhomogeneity during ESD procedure is transient. On the other hand, intraoperative visualization of ventilation is currently emerging topic but is lack of evidence. Our findings suggest that EIT may be a promising clinical tool for continuous and noninvasive monitoring of pulmonary status in mechanically ventilated patients with lateral position during surgery. The insight knowledge gained from the current manuscript may provide clinical practice for intraoperative application of this new technology in future. These are the important findings and clinical values of our study, which are stated in the manuscript (See page 19 line 12-21).

We strongly agree with the reviewer's comment that perfusion and matching on V/Q are also important for final gas exchange. Freichs, et al (*Regional Lung Perfusion as Determined by Electrical Impedance Tomography in Comparison With Electron Beam CT Imaging. IEEE Trans Med Imaging. 2002 Jun;21(6):646-52.)* have found that EIT imaging of lung perfusion is feasible when an electrical impedance contrast agent is used. Further investigations in perfusion and V/Q measurement using EIT are inevitable. We have added this as a limitation in the revised manuscript (See page 19 line 5-6).

Detail description of maintenance of anaesthesia is presented in Methods section of revised manuscript (See page 9 line 4-6).

Changes in the text:

Page 19 line 12-21: In patients with left lateral position undergoing ESD, left lung was characterized by decreased ventilation and more inhomogeneity while right lung was opposite after intubation. ESD procedure did not lead to significant changes in either regional ventilation distribution or homogeneity. After extubation, regional homogeneity returned to the level before anesthesia, supporting the notion that the effect of ESD operation with carbon dioxide insufflation and general anesthesia in left lateral positioning on lung condition is transient. Therefore, EIT may be a promising clinical tool for continuous and noninvasive monitoring of pulmonary status that can be especially useful in mechanically ventilated patients with left lateral position during surgery. More clinical validation studies are awaited to explore the full potential of the technology.

Page 19 line 5-6: We also did not measure lung perfusion using EIT, as matching

on V/Q is also important for final gas exchange.

Page 9 line 4-6: Propofol at the rate of 3-7 $mg \cdot kg^{-1} \cdot h^{-1}$, cisatracurium 2-3 $ug \cdot kg^{-1} \cdot min^{-1}$ and remifentanil 0.2 $ug \cdot kg^{-1} \cdot min^{-1}$ were continued to maintain anesthesia. And sufentanil was intermittently administered during surgery.

6. **After all how does it affect the clinical outcome that was not measured or evaluated. Mere only experimental venture using sophisticated gadget without benefitting clinically is a waste of resource.**

Reply: To address the reviewer's concern, the data regarding the clinical outcomes using EIT monitoring has now been added in our revised text (See page 14 line 4-8 and page 31 Table 3).

Changes in the text: Page 14 line 4-8: Clinical outcomes: Summary of clinical outcomes is shown in Table 3. No patient was detected with postoperative hypoxemia, cough, pulmonary edema, pneumonia or atelectasis. Two patients (9%) had fever after surgery. In addition, no patient was treated with atomization inhalation or transferred to intensive care unit postoperatively.

Table 3 Clinical outcomes for 22 patients undergoing ESD in left lateral position

	Number	Percentage
Hypoxemia	0	0
Fever	2	9%
Cough	0	0
Pulmonary edema	0	0
Pneumonia	0	0
Atelectasis	0	0
Atomization inhalation treatment	0	0
Transfer to intensive care unit	0	0

7. **You have discussed the optimization of ventilation based on EIT but have not approached it. What is the point then?**

Reply: Thanks for this constructive suggestion. We totally agree with the reviewer's opinion on the great value of optimization of ventilation based on EIT. In our team, another part of research is conducting to compare different EIT-guided ventilation settings to evaluate the optimization of ventilation in patients undergoing ESD. We have mentioned this as a limitation in the last paragraph of our submitted manuscript (See page 19 line 3-5). While, the study submitted here firstly found that ESD procedure with carbon dioxide insufflation did not lead to significant changes in either regional ventilation or homogeneity, and the change of lung inhomogeneity during ESD procedure is transient. These results have not been previously published. Our findings suggest that EIT may be a promising clinical tool for noninvasive and bedside real-time monitoring of pulmonary status in patients with lateral position during surgery. Therefore, this study provides new clue for clinical application of this technology on intraoperatively monitor the real-time changes of lung condition in future.

8. Even omission of PEEP is a well-known cause of ventilation induced atelectasis. What about that?

Reply: In this study, there was no ventilation induced atelectasis occurred in 22 patients (See page 14 line 5-6).

Changes in the text: Page 14 line 5-6: No patient was detected with postoperative hypoxemia, cough, pulmonary edema, pneumonia or atelectasis.

Impression: Good currently emerging and relevant topic chosen which is the strength of this observational study. However, low power, lack of control group and absence of outcome evaluation put question on utility of this sophisticated gadget. However, I can give another look provided the authors come back with suitable answer.