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RE: Manuscript ID: 62543

Dear Editor，

We would like to thank the editor for giving us a chance to resubmit the paper, and also thank the reviewer for giving us constructive suggestions which would help us both in English and in depth to improve the quality of the paper. Here we submit a new version of our manuscript with the title "**Asymptomatic carbon dioxide embolism during transoral vestibular thyroidectomy: A case report and literature review**", which has been modified according to the reviewer's suggestions. Efforts were also made to correct the mistakes and improve the English of the manuscript. We mark all the changes in blue in the revised manuscript.

Sincerely yours,

Jiaxi Tang MD

The following is a point-to-point response to the reviewer's comments.

Reviewer #1:

General comments:

1. This manuscript describes a single case of presumed carbon dioxide embolus (CDE) associated with carbon dioxide insufflation during endoscopic thyroidectomy. The manuscript has value in that

it introduces a new clinical concept to anesthesiologists and surgeons who might be unaware of this possible condition. 2. The incidence of CDE is unknown with this surgical procedure, and the authors miss a great opportunity to inform readers how this might be quantified, and how the risk of CDE affects the risk-to-benefit profile of endoscopic thyroidectomy. I have discussed this further in the Specific Comments to the authors. 3. The Discussion is strikingly similar to an editorial published by Lanier and Warner on CDE in another form of endoscopic surgery. (See: Lanier WL, Warner MA. Assessing acceptable risk in new surgical procedures, with special reference to gas emboli in transanal total mesorectal surgery. Dis Colon Rectum. 62:777-780, 2019.) The authors should acknowledge that editorial and its relationship to the current report. 4. The manuscript, particularly the Discussion, is excessively long, and the concepts in the Introduction and Discussion repeat themselves. This needs to be tidied up. 5. The authors tend to "cherry pick" the literature in their discussion. On one hand, they get into the implications of one form of anesthesia versus another, the use of intravascular and positive end-expiratory airway pressure (presumably to increase central venous pressure), which are probably not that important…as I will explain to the Specific Comments. However, they miss an opportunity better describe detection of CDE and differentiate it from similar clinical scenarios. 6. In reality, this manuscript has two portions of original data. The authors place the second part within the Discussion. This needs to be moved out to a separate Methods and Results section. 7. I am a bit surprised that the authors were able to hear both systolic and diastolic murmurs when the patient's hemodynamics appeared to be unaltered. 8. I think the authors could do a better job of introducing the importance of pressor drugs and applying the concepts of The American Heart Association's guidelines for advanced cardiac life support if there is a catastrophic carbon dioxide embolus.

Answer: Thank you for the comments on the paper. Thanks for your affirmation of this article. We have carefully read the relevant literature recommended by you. We have revised the manuscript as suggested since we consider that some sentences or descriptions in the Discussion part are not so accurate based on the literature. In addition, we have adjusted the structure of the manuscript based on the reviewer's suggestions.

1. This manuscript describes a single case of presumed carbon dioxide embolus (CDE) associated with carbon dioxide insufflation during endoscopic thyroidectomy. The manuscript has value in that it introduces a new clinical concept to anesthesiologists and surgeons who might be unaware of this possible condition.

Answer: Thank you for the comments on the paper. Thanks for your affirmation of this article.

2. The incidence of CDE is unknown with this surgical procedure, and the authors miss a great opportunity to inform readers how this might be quantified, and how the risk of CDE affects the risk-to-benefit profile of endoscopic thyroidectomy. I have discussed this further in the Specific Comments to the authors.

Answer: Thank you very much for your enlightening suggestions. From the prospective study of a small sample of 81 patients by Fu et al., we calculated that the incidence of CDE in transoral endoscopic thyroidectomy was approximately 2.4%. (See: Transoral Endoscopic Thyroidectomy: Review of 81 Cases in a Single Institute. Journal of Laparoendoscopic & Advanced Surgical Techniques Part A. 2018 .) However, due to the small sample size of the study, accurate morbidity and risk-to-benefit profile cannot be given. As discussed by Lanier and Warner, (See: Lanier WL, Warner MA. Assessing acceptable risk in new surgical procedures, with special reference to gas emboli in transanal total mesorectal surgery. Dis Colon Rectum. 62:777-780, 2019.), we also agree with that a long term, high-volume, prospective study is required to accurately quantify the incidence of CDE in endoscopic thyroidectomy (using reference standard monitoring) and its consequences. (Page 8 line 18-24).

3. The Discussion is strikingly similar to an editorial published by Lanier and Warner on CDE in another form of endoscopic surgery. (See: Lanier WL, Warner MA. Assessing acceptable risk in new surgical procedures, with special reference to gas emboli in transanal total mesorectal surgery. Dis Colon Rectum. 62:777-780, 2019.) The authors should acknowledge that editorial and its relationship to the current report.

Answer: Thank you very much for the reviewer's serious and responsible attitude, which is of great help to the rigor of the paper publication. The editorial written by Lanier WL and Warner MA, mainly points out the deficiencies of the research of Dickson et al. They analyzed the susceptibility factors of CO2 embolism in TaTME surgery, explained the clinical manifestations of CO2 embolism, and proposed that the methods to avoid the occurrence and death of CO2 embolism are prevention, standardized monitoring, and timely diagnosis and treatment. Finally, they proposed that in the study of TaTME surgery, multi-disciplinary personnel should work together to avoid interference with the results of the trial by conflict of interest, obtain accurate test data and ensure patient safety.

The discussion part of our report mainly discusses the current commonly used diagnostic methods for carbon dioxide embolism, explains the mechanism of the increase and decrease of ETCO2 in carbon dioxide embolism, and explains the possible reasons for the stable vital signs of our patients after carbon dioxide embolism. In order to better understand the characteristics of carbon dioxide embolization in endoscopic thyroid surgery, we systematically searched the reports of carbon dioxide embolization in endoscopic thyroid surgery in the past 10 years, and concluded that the incidence of this type of surgery is low and can occur at any time during the operation. The prognosis is generally good. Our purpose is to remind medical staff that when diagnosing carbon dioxide embolism, elevated ETCO2 may be a very helpful indicator. We recommend the comprehensive use of multiple monitoring methods to detect carbon dioxide embolism in time and deal with it in time.

This editorial is similar to our report in recommending the comprehensive use of monitoring methods to diagnose and treat carbon dioxide embolism in a timely manner. The two reports are obviously different in the type of surgery discussed and the focus of the discussion.

4. The manuscript, particularly the Discussion, is excessively long, and the concepts in the Introduction and Discussion repeat themselves. This needs to be tidied up.

Answer: Thank you very much for the pertinent comments of the reviewer, which will greatly help improve the quality of our article. We have removed some duplicate content.

5. The authors tend to “cherry pick” the literature in their discussion. On one hand, they get into the implications of one form of anesthesia versus another, the use of intravascular and positive end-expiratory airway pressure (presumably to increase central venous pressure), which are probably not that important…as I will explain to the Specific Comments. However, they miss an opportunity better describe detection of CDE and differentiate it from similar clinical scenarios.

Answer: Thanks to the reviewers for their comments, which will greatly help improve the rigor of our article. We are also aware that some of the opinions in our article are not accurate, and we will delete this part of the content. In addition, in the differential diagnosis CDE, our description is not adequate, we will elaborate on the situation of our patients. (Page 10 line 13-22).

6. In reality, this manuscript has two portions of original data. The authors place the second part within the Discussion. This needs to be moved out to a separate Methods and Results section.

Answer: Thanks for the reviewer’s comment, we very much agree with your suggestion. We will reformat the second part of the original data according to the reviewer's recommendations. (Page 7 line 13-29; Page 8 line1-29).

7. I am a bit surprised that the authors were able to hear both systolic and diastolic murmurs when the patient’s hemodynamics appeared to be unaltered.

Answer: Thanks to the reviewer for reviewing our article, and gave us a lot of valuable comments, which played a very important role in improving the logic and depth of our article. Our patient had a sudden violent rise in ETCO2 during the operation. We immediately considered the occurrence of ETCO2 embolism or pneumothorax. We stopped the CO2 injection as soon as possible. Since the patient's vital signs are stable, we auscultated the patient's lung and heart sounds as soon as possible, and we did hear a coarse precardiac murmur. As mentioned by Shulman D and Aronson HB, typical precordial murmurs can appear before clinical manifestations. (See: Shulman D, Aronson HB. Capnography in the early diagnosis of carbon dioxide embolism during laparoscopy. Can Anaesth Soc J. 1984. 31(4): 455-9.) Finally, I would like to thank the reviewer for your doubt. We checked the literature again and gained a deeper understanding of this phenomenon. (Page 10 line 11-13).

8. I think the authors could do a better job of introducing the importance of pressor drugs and applying the concepts of The American Heart Association’s guidelines for advanced cardiac life support if there is a catastrophic carbon dioxide embolus.

Answer: Yes, we strongly agree with you. We have revised the manuscript as suggested since we consider that this part in the "Discussion" section is not clear enough. (Page 11 line 3-11).

Specific Comments:

P 1, LM 16, and P 6, LM 13-15: As discussed by Lanier and Warner, gas embolus during endoscopic surgery does not require an identified (or even identifiable) venous injury. P 1, LM 26-27, and P 9, LM 15-17: Given the minimal effects of one anesthetic versus another on blood flow distribution within the body, I seriously doubt that one anesthetic technique versus another is going to affect outcomes during carbon dioxide embolus. To my way of thinking, the predominant factors in dictating outcomes are the volume and rate of gas entered into the circulation, not what anesthetic was present when that occurred. Focusing on anesthetic technique would, in my opinion, lead to a false sense of security. P 2, LM 20: Consider rewording the colloquial “game changer.” P 3, LM 17: Wouldn’t “chest roentgenogram” be preferable to “chest X-ray”? P 3, LM 28: This passage makes it sound like the frenulum is a part of the lower lip. Please reword the passage for clarity, and stick to anatomic terms (eg, superior, inferior, anterior, etc.), not “above,” which will change as the patient’s position changes. P 4, LM 1: Replace “normal saline” with “0.9% saline solution.” P 4, LM 2: Place a comma before “was,” for clarity. P 4, LM 21: The time course of the return of ETCO2 is interesting. P 5, LM 9-10 and beyond: Inasmuch as most of the concepts within the Discussion are not unique to endoscopic thyroid surgery, I suggest that the authors give consideration to beginning their Discussion with a passage such as this: “Endoscopic surgical techniques, including those that involve insufflation of the tissues with carbon dioxide, are gaining wider acceptance and use worldwide. These advances have introduced the possibility of carbon dioxide embolus (including life-threatening embolus). Such factors introduce challenges in preventing, diagnosing, and treating carbon dioxide embolus, and determining how the risk of embolus affects the risk-to-benefit profile of any new surgical procedure. These issues have recently been reviewed by Lanier and Warner, as related to colorectal surgery. We will discuss some of these same issues as they apply to endoscopic thyroid surgery.” (The reference mentioned is: (See: Lanier WL, Warner MA. Assessing acceptable risk in new surgical procedures, with special reference to gas emboli in transanal total mesorectal surgery. Dis Colon Rectum. 62:777-780, 2019.) P 6, LM 14: “Veres needles” is an arcane term. Can you use more universally understood terminology? P 6, LM 23-

P 7, LM 1: This information appears to be repeated elsewhere in the manuscript.

P 7, LM 7 to P 8, LM 14: Here, the authors are describing a separate study. This information should be included in a Methods section (P 7, LM 7 to LM 20) and a Results section (P 7, LM 20 onward). The latter portions of this second segment might even belong in the Discussion regarding discussing the new Methods and Results. P 8, LM 9-10: Please distinguish between the Trendelenburg and left lateral decubitus positions. As such, this word "Trendelenburg" is misplaced. Additionally, please discuss what you hope to achieve by the left lateral decubitus position with the head down. You only mention the head-down portion in your original report. P 8, LM 20-23: I simply find it difficult to believe that this concept has been proven using a sound study design and adequate statistical power. I could be wrong, but I'd still recommend deleting this from the Discussion. P 8, LM 28-P 9, LM 1: The concept of applying positive end-expiratory pressure and expanding intravenous volume, relates to a tired, and largely erroneous, concept that it is possible to increase venous pressure and prevent further embolus. Such a concept ignores the fact that increases in intrathoracic pressure and central venous pressure are somewhat ineffective in altering extrathoracic venous pressures. Further, these concepts ignore the Venturi effect and other mechanisms by which gasses can enter the venous system by methods other than arithmetic changes in central venous pressure. For further discussion, the authors should see both the Lanier and Warner editorial referenced above, as well as this article: Lanier WL, Albrecht RF II, Iaizzo PA: Divergence of intracranial and central venous pressures in lightly anesthetized, tracheally intubated dogs that move in response to a noxious stimulus. Anesthesiology 84:605-613, 1996. P 9, LM 5: Change "inhaling" to "aspirating." Figure 2: This figure needs a better legend to describe the two parts and arrows to identify key anatomic features. Otherwise, it is difficult to determine what is going on in the first part of the figure. For the first couple of readings, I thought I was looking a surgeon's glove, not the patient's chin and neck. Table1: "Age" should have units of measurement. Expand to "Reduce INSUFFLATION pressure," "precordial Doppler SONOGRAPHY," and "Aggressive INTRAVENOUS volume expansion."

Answer: Thank you for the comments on the paper. We have revised the manuscript as suggested.

P 1, LM 16, and P 6, LM 13-15: As discussed by Lanier and Warner, gas embolus during endoscopic surgery does not require an identified (or even identifiable) venous injury.

Answer: Yes, we awfully agree with you. Neither direct knowledge of venous injury nor visible bleeding are not prerequisite for the diagnosis of CDE or GE. But just as Lanier et al. said, gas can enter a vein anytime there is a rent in the vessel. We described the rupture of the anterior jugular vein in our patient during the operation, but we did not regard significant bleeding as a necessary condition for the diagnosis of CDE. Finally, thank you again for the reminder.

P 1, LM 26-27, and P 9, LM 15-17: Given the minimal effects of one anesthetic versus another on blood flow distribution within the body, I seriously doubt that one anesthetic technique versus another is going to affect outcomes during carbon dioxide embolus. To my way of thinking, the predominant factors in dictating outcomes are the volume and rate of gas entered into the circulation, not what anesthetic was present when that occurred. Focusing on anesthetic technique would, in my opinion, lead to a false sense of security.

Answer: Yes, your opinions inspired us and we have deleted this controversial content.

P 2, LM 20: Consider rewording the colloquial “game changer.”

Answer: Thank the reviewer for the comments. We have used more professional vocabulary to replace the previous inappropriate words. (Page 4 line 12-13).

P 3, LM 17: Wouldn’t “chest roentgenogram” be preferable to “chest X-ray”?

Answer: Yes, we awfully agree with you and we revised the manuscript accordingly. In addition, we added the immediate postoperative chest roentgenogram results that we missed in the Imaging examinations. (Page 5 line 21-23; page 6 line28; page 10 line 20; page 17 line 2).

P 3, LM 28: This passage makes it sound like the frenulum is a part of the lower lip. Please reword the passage for clarity, and stick to anatomic terms (eg, superior, inferior, anterior, etc.), not “above,” which will change as the patient’s position changes.

Answer: Thanks to the reviewer for your comments and pointed out the inaccuracy of our words. This is of great help in improving the quality of our articles. We have revised the manuscript accordingly. (Page 6 line 5).

P 4, LM 1: Replace “normal saline” with “0.9% saline solution.”

Answer: Thank you for the comments on the paper. We have revised the manuscript as suggested. (Page 6 line 6-7).

P 4, LM 2: Place a comma before “was,” for clarity.

Answer: Thanks to the reviewers for their serious and rigorous attitude, which has greatly helped improve the quality of our articles. We have revised the manuscript as suggested. (Page 6 line 7).

P 4, LM 21: The time course of the return of ETCO2 is interesting.

Answer: Yes, your opinions inspired us and we have supplemented the details of this part. (Page 6 line 24-26).

P 5, LM 9-10 and beyond: Inasmuch as most of the concepts within the Discussion are not unique to endoscopic thyroid surgery, I suggest that the authors give consideration to beginning their Discussion with a passage such as this: “Endoscopic surgical techniques, including those that involve insufflation of the tissues with carbon dioxide, are gaining wider acceptance and use worldwide. These advances have introduced the possibility of carbon dioxide embolus (including life-threatening embolus). Such factors introduce challenges in preventing, diagnosing, and treating carbon dioxide embolus, and determining how the risk of embolus affects the risk-to-benefit profile of any new surgical procedure. These issues have recently been reviewed by Lanier and Warner, as related to colorectal surgery. We will discuss some of these same issues as they apply to endoscopic thyroid surgery." (The reference mentioned is: (See: Lanier WL, Warner MA. Assessing acceptable risk in new surgical procedures, with special reference to gas emboli in transanal total mesorectal surgery. Dis Colon Rectum. 62:777-780, 2019.)

Answer: Thank you very much for your warm suggestions. This is very helpful to improve the depth and logic of our article. We have revised the manuscript as suggested and rearranged the structure of the article. (Page 7 line 3-29; page 10 line1-22).

P 6, LM 14: "Veres needles" is an arcane term. Can you use more universally understood terminology?

Answer: Yes, we agree with you. We have used more universally understood terminology. (Page 9 line 12).

P 6, LM 23-P 7, LM 1: This information appears to be repeated elsewhere in the manuscript.

Answer: Yes, we agree with you. Thank you for your careful correction, we have deleted this part of the duplicate content.

P 7, LM 7 to P 8, LM 14: Here, the authors are describing a separate study. This information should be included in a Methods section (P 7, LM 7 to LM 20) and a Results section (P 7, LM 20 onward). The latter portions of this second segment might even belong in the Discussion regarding discussing the new Methods and Results.

Answer: Thank you very much for your enlightening suggestions. This has a great effect on improving the quality of our articles. We have revised the manuscript as suggested and rearranged the structure of the article. (Page 7 line 13-29; Page 8 line1-29).

P 8, LM 9-10: Please distinguish between the Trendelenburg and left lateral decubitus positions. As such, this word "Trendelenburg" is misplaced. Additionally, please discuss what you hope to achieve by the left lateral decubitus position with the head down. You only mention the head-down portion in your original report.

Answer: Thank you for your comments and reminders. We have corrected our previous misunderstanding and discussed the clinical significance of this position. (Page 6 line 22; Page 7 line7; page 8 line 15; page 11 line 1; attachment: Table File).

P 8, LM 20-23: I simply find it difficult to believe that this concept has been proven using a sound study design and adequate statistical power. I could be wrong, but I'd still recommend deleting this from the Discussion.

Answer: Thanks for the reviewer's comment. We deleted the content that was controversial.

P 8, LM 28-P 9, LM 1: The concept of applying positive end-expiratory pressure and expanding intravenous volume, relates to a tired, and largely erroneous, concept that it is possible to increase venous pressure and prevent further embolus. Such a concept ignores the fact that increases in intrathoracic pressure and central venous pressure are somewhat ineffective in altering extrathoracic venous pressures. Further, these concepts ignore the Venturi effect and other mechanisms by which gasses can enter the venous system by methods other than arithmetic changes in central venous pressure. For further discussion, the authors should see both the Lanier and Warner editorial referenced above, as well as this article: Lanier WL, Albrecht RF II, Iaizzo PA: Divergence of intracranial and central venous pressures in lightly anesthetized, tracheally intubated dogs that move in response to a noxious stimulus. Anesthesiology 84:605-613, 1996.

Answer: Thanks for the reviewer's comment. We have carefully read the literature recommended by the reviewer, and we have deleted the content that is controversial.

P 9, LM 5: Change "inhaling" to "aspirating."

Answer: Thank you for your comment. We have revised the manuscript as suggested. (Page 11 line

2).

Figure 2: This figure needs a better legend to describe the two parts and arrows to identify key anatomic features. Otherwise, it is difficult to determine what is going on in the first part of the figure. For the first couple of readings, I thought I was looking a surgeon's glove, not the patient's chin and neck.

Answer: Thank you for your comments and reminders. We have revised the manuscript as suggested. (Page 17 line 3-5).

Table1: "Age" should have units of measurement. Expand to "Reduce INSUFFLATION pressure," "precordial Doppler SONOGRAPHY," and "Aggressive INTRAVENOUS volume expansion."

Answer: Thank you for your comments and reminders. This is very helpful to improve the quality of our article. We have revised the manuscript as suggested. (See attachment: Table File)