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Review Comments

Reviewer A

Thank you for inviting me to review this paper. This review article outlines a current situation regarding anesthesia for surgery of large mediastinum tumors. Surgery for thoracic mediastinal giant tumors is rare, and various considerations must be taken into account for both surgery and anesthesia. This report summarizes the preoperative, intraoperative, and postoperative points regarding anesthesia during resection of thoracic mediastinal giant tumors. I think that this review report may be useful and considered potentially acceptable for the MEDIASTINUM. However, the impact of the contents presented by current format is considered somewhat weak, so I would like authors to consider and revise following points.

REPLY: We are very grateful to the reviewer for these helpful comments. We have tried to respond to all her/his remarks as follows.

1. The contents are extracted from various reviews that have been published. Some of the information may be a little out of date. Also, the structure of the paper appears to be similar to Reference 3, so please check it out.

REPLY 1. We really thank the reviewer for the precious advice. As giant mediastinal masses are rare entities, we were able to retrieve a limited bibliography on the subject, mainly retrospective. We tried to give an insight into the most updated anesthesia planning in the management of complex cases with high risks of cardiorespiratory derangement. We stressed the importance of careful preoperative planning we reformatted the manuscript extensively and accordingly.

2. Line 150. Regarding ECMO, in the case of malignant tumors, there is a general concern that the use of ECMO may lead to systemic seeding of tumor cells. Please discuss and comment on this. Also, please provide efficient uses and differences between VA-ECMO and VV-ECMO.

REPLY 2. We really thank the reviewer to pointing this out, in fact the outcome in thoracic oncologic patients treated with ECMO is variable and the management should be tailored on the individual case. We modified the text accordingly which now reads:

Line 399 - Extracorporeal membrane oxygenation (ECMO) is used to treat severe cardiopulmonary failure, but it is not yet known whether it is also appropriate for use in patients with cancer. Thoracic neoplasms are distinct from other malignant tumors because they may have a direct effect on cardiopulmonary function, nevertheless as observational and registry analysis could not provide a clear recommendation pro or contra ECMO application, focus on tailored patient selection should pursued to achieve optimal results [12–14].

Line 684 - Veno-arterial ECMO should be preferred in compromised patients with giant mediastinal masses and high risk of respiratory and hemodynamic collapse. Therefore, veno-venous ECMO should be applied in selected cases of patients with isolated respiratory symptoms and airway compression.

3. Line 211. Please indicate what NIRS stands for.

REPLY 3. NIRS stands for "Near Infrared Spectroscopy". We modified the text accordingly which now reads:

Line 840 - Near Infrared Spectroscopy (NIRS) monitoring to assess any worsening of the SVCS-induced cerebral edema.

4. Line 215. Regarding induction of anesthesia, it is mentioned that it is best to maintain spontaneous breathing during induction of anesthesia, and I agree with this. On the other hand, there are some cases where muscle relaxants can be used more safely. Please consider this and comment.

REPLY 4. We really thank the reviewer for pointing this out. We modified the text and provided new reference *(Hartigan, P. M., Karamnov, S. et al. 2021 Mediastinal Masses, Anesthetic Interventions, and Airway Compression in Adults: A Prospective Observational Study. Anesthesiology, 136(1), 104–114. https://doi.org/10.1097/aln.0000000000004011).*

The text now reads as follows:

Line 854 - Nevertheless, as surgery often requires neuromuscular blockade, using short-acting paralyzers, such as succinylcholine or rocuronium, as its antidote; sugammadex is currently available seems a convenient choice to return to spontaneous ventilation in case of severe airway collapse or hemodynamic instability.

Recently, *Hartigan and colleagues* demonstrated that neuromuscular blockade did not induce airway collapse or difficult ventilation in patients with mediastinal masses presenting different grades of airway stenosis [27]. Nevertheless, the study included only seventeen patients. Furthermore, patients could be excluded from the study according to the attending anesthesiologists' choice, maybe creating a selection bias.

If the loss of spontaneous breathing exacerbates cardiorespiratory collapse in fact, the first step should be the rapid reversal of neuromuscular blockade. Meanwhile, the patient should be placed in her/his "rescue position" (if there is one), and ventilation should be attempted using a rigid bronchoscope. Unfortunately, a rigid bronchoscope can overcome tracheal compression but it hardly restores adequate ventilation in case of compression at the level of the bronchial branches.

5. Line 217. When induction of anesthesia is performed with maintain of spontaneous breathing, the use of remifentanil may cause muscle stiffness, which may lead to ventilatory difficulties. Please discuss and comment on this point.

REPLY 5. We really thank the reviewer for this comment and kind suggestion. We have therefore modified the manuscript as follows:

Line 844 - Induction of anesthesia requires a stepwise approach. An effective way to secure the airways is awake fiberoptic intubation with the patient in spontaneous breathing. Topic anesthesia and intravenous drugs with a short half-life (remifentanil, dexmedetomidine, ketamine) guarantee the achievement of oro-tracheal intubation with an excellent level of security. Remifentanil boluses that could exacerbate stiffness, compromising patient ventilation and subsequent intubation should be avoided.

6. Line 226. The use of succinylcholine during induction of general anesthesia has become less common in recent years. Blood K levels increase after succinylcholine use, and recovery time from muscle relaxation is faster with rocuronium and subsequent use of Bridion (sugammadex sodium) than with succinylcholine. Please mention this point.

REPLY 6. We fully agree with this remark, thank you. The text now reads:

Line 854 - Nevertheless, as surgery often requires neuromuscular blockade, using short-acting paralyzers, such as succinylcholine or rocuronium, as its antidote; sugammadex is currently available seems a convenient choice to return to spontaneous ventilation in case of severe airway collapse or hemodynamic instability.

7. Line 244. Please comment on the need for postoperative monitoring even in “safe” cases.

REPLY 7. Thank you for the suggestion. We added postoperative planning for patients classified as "safe".

The text has been modified as follows:

Line 851 - *Safe* patients should be promptly extubated at the end of surgery and require sub-intensive care monitoring for at least 24 hours in case of no intraoperative complications.

8. Line 250. It is stated that only two drugs, ketamine and pregabalin, are recommended for postoperative pain management. Please mention the effectiveness of not only these two drugs, but also a variety of other ones.

REPLY 8. We really thank the reviewer for raising such an important matter. We agree with the reviewer that "multimodal analgesia" may include different types of drugs and locoregional techniques. We changed the manuscript including several other post operative analgesic strategies. The text now reads:

Line 856 - Nevertheless, adequate pain management is essential to ensure rapid extubation and rehabilitation. One of the most effective approaches is multimodal and opioid-sparing analgesia [28]. Several medications in combination with local anesthetics seem to have a good profile in reducing the opioids needed after thoracic surgery: ketoprofen, ketorolac, paracetamol, pethidine, flurbiprofen, dexmedetomidine [29]. Among others, ketamine demonstrated a statistically significant reduction in acute post-thoracotomy pain but low power as a preventative agent for chronic post-thoracotomy pain [30] as well as pregabalin significantly reduced pain scores, decreasing postoperative neuropathic pain and morphine consumption [31].

9. I would like the authors to mention about the following points: This type of rare surgery should be carefully planned by surgeons, anesthesiologists, and other multidisciplinary professionals at the institutional board, and the surgery should be performed with the consent of all involved in the surgery. Surgery and anesthesia should be prepared in advance for intraoperative events that rarely occur. In addition to the large size of the tumor, it is better for the anesthesiologist to have a preoperative discussion with the surgeon regarding the oncological characteristics of the tumor, because the oncological characteristics of the tumor have a significant impact on the surgery. There is an interesting report in MEDIASTINUM that discusses these issues from the perspective of medical safety. I would like the authors to cite the following article:

Sakakura N, Nakai A, Suda H, Nakada T, Matsui T, Nakanishi K, Shirai S, Nakada J, Horio Y, Oya Y, Takahashi Y, Kuroda H. Life-threatening massive bleeding in the pulmonary trunk adjacent to the right ventricular outflow tract during the resection of a large mediastinal germ cell tumor: proposed safety measures in the absence of cardiovascular surgeons: a case report. Mediastinum. 2021 Jun 25;5:19. doi: 10.21037/med-20-66.

Please consider the above to the extent possible. I hope my comments will be of some help.

Thank you again for the opportunity to review this interesting work.

REPLY 9. We really thank the reviewer for this comment and kind words of appreciation. We believe preoperative planning is the pivotal element when faced with rare entities like giant mediastinal masses. Preoperative discussion should include anesthesiologists, surgeons, and oncologist. We agree that the tumor characteristics have a high impact on the surgical decision

and correlated complications. We read with great interest the work of Sakakura and colleagues which describes a case of intraoperative complication in the absence of the right reference figure to face the problem (a cardio-surgeon).

We decided to change the text as follows:

Line 393 - Preoperative planning is the cornerstone in managing patients with giant mediastinal masses. Perioperative discussion should involve anesthesiologists, surgeons and oncologists. All professionals should agree on the proposed treatment and alternative strategies in case of intraoperative drawbacks. Creating a multidisciplinary discussion may reduce the risk of life-threatening complications [11].

Reviewer B

The reviewer is honored to review an article reviewing the anesthetic management for giant mediastinal tumor surgery. This paper is well written and it provides meaningful information concisely in terms of a review article; however, it does not include any figures and tables. Addition of some figures and/or tables would surely make this manuscript more interesting for the potential readers. For example, any pictures of CT images and/or intraoperative procedures would help the potential readers to understand the contents of the manuscript correctly. In this meaning, the reviewer strongly suggests that the authors should provide a couple of figures and tables in each section of this manuscript. However, overall, this paper is well organized review, and therefore, it can be potentially published in the journal.

Regarding references, please conform to the author instruction.

REPLY. We really thank the reviewer for her/his comment, and kind words of appreciation.

We agree that adding radiological images may create a more attractive work. We added two tables (see Tables 2 and 3) and three figures (two radiological images and a transesophageal echocardiography image). We also reformatted the references as per journal fashion.

Reviewer C

The authors are congratulated for tackling a topic of significant clinical importance, but limited evidence. The review is largely opinion, but that is inevitable in the absence of data. My chief criticism is that the criteria for decision-making is too vague.

REPLY. We really thank the reviewer for her/his comments and suggestions to improve the manuscript.

We tried to give an answer to all points.

In Table 1, "Safe" is defined as "negative CT scan". Does this imply that ANY amount of airway/vessel compression would shift the patient to "Uncertain" category?

We fully agree that "negative CT scan" is too generic and it may generate confusion among the readers. So we decided to modify the criteria, going more in-depth. Please See Table 1 (modified

In line 172 (pg 4) the authors refer to criteria of Qanadli, et al, and You, et al, as critical to the decision to use ECMO, without explaining what those criteria are. They should be explained.

Readers may be misled to think that ECMO cannulation is recommended for even very minor CT evidence of compression. The weakness of the evidence supporting a 50% rule should be highlighted (Shamberger, et al).

We created tables to show Qanadli and colleagues and Yu and colleagues' criteria. Please See Table 2 and Table 3

Also - (Pg 5 Line 215) Are the authors recommending awake intubation in ALL patients? What about those with minor equivocal symptoms and minor findings on CT?

We really thank the reviewer for pointing this out. The recommendation for awake intubation in all patients with symptoms, airway compression at CT scan (maybe even if less than 50% of the cross-sectional area) or in all cases where clinicians may expect difficulties in ventilation or intubation mainly depends on center experience and the thoracic team protocols. We modified the text which now reads:

Line 844 - Induction of anesthesia requires a stepwise approach. Depending on local protocols and anetshesiologist’s experience, an effective way to secure the airways is awake fiberoptic intubation with the patient in spontaneous breathing. Topic anesthesia and intravenous drugs with a short half-life (remifentanil, dexmedetomidine, ketamine) guarantee the achievement of oro-tracheal intubation with an excellent level of security. Remifentanil boluses that could

exacerbate stiffness, compromising patient ventilation and subsequent intubation should be avoided.

The endotracheal tube should be the largest possible to resist extrinsic compressions. We may use spiral-reinforced endotracheal or dual-lumen tubes if the surgeon requires them. Subsequently, the anesthetic plan should be deepened gradually to keep the patient breathing spontaneously. The maintenance of spontaneous breathing or pressure support ventilation avoids a significant increase in pleural pressure, decreasing the compressing effects of the mediastinal mass.

The authors also repeat the recommendation to maintain spontaneous breathing, as has been repeated in other reviews, but has recently been challenged (Hartigan PM, et al, Anesthesiology 2022), and this controversy should be acknowledged. I would also challenge the recommendation to rescue patients first by assuming the preferred position, then adding rigid bronchoscopy. This is impractical in the lateral or prone patient.

We really thank the reviewer for her/his suggestions and we read with great interest the work suggested by the reviewer. We decided to incorporate it in the manuscript.

Now the text reads as follows:

Line 855 - Nevertheless, as surgery often requires neuromuscular blockade, using short-acting paralyzers, such as succinylcholine or rocuronium, as its antidote; sugammadex is currently available seems a convenient choice to return to spontaneous ventilation in case of severe airway collapse or hemodynamic instability.

Recently, *Hartigan and colleagues* demonstrated that neuromuscular blockade did not induce airway collapse or difficult ventilation in patients with mediastinal masses presenting different grades of airway stenosis [27]. Nevertheless, the study included only seventeen patients. Furthermore, patients could be excluded from the study according to the attending anesthesiologists' choice, maybe creating a selection bias.

If the loss of spontaneous breathing exacerbates cardiorespiratory collapse in fact, the first step should be the rapid reversal of neuromuscular blockade. Meanwhile, the patient should be placed in her/his "rescue position" (if there is one), and ventilation should be attempted using a rigid bronchoscope. Unfortunately, a rigid bronchoscope can overcome tracheal compression but it hardly restores adequate ventilation in case of compression at the level of the bronchial branches.

Line 902 - If the loss of spontaneous breathing exacerbates cardiorespiratory collapse in fact, the first step should be the rapid reversal of neuromuscular blockade. Meanwhile, the patient should be placed in her/his "rescue position" (if there is one), and ventilation should be attempted using a rigid bronchoscope. Unfortunately, a rigid bronchoscope can overcome tracheal compression but it hardly restores adequate ventilation in case of compression at the level of the bronchial branches.

The recommendation for a trans pulmonary thermodilutionsystem (? PA line) seems unjustified to me, but I acknowledge that this is a collection of opinions.

REPLY: We fully agree with the reviewer regarding the use of trans-pulmonary thermodilution as the first method of hemodynamic monitoring we then now write this in the manuscript:

1. Anaesthetic monitoring:
    - Hemodynamic monitoring: transpulmonary thermodilution systems or pulse-contour analysis to monitor cardiac function continuously should be applied.
    - Transesophageal echocardiography (TEE) should be used when available especially in previously evaluated patients with systolic or diastolic dysfunction, pericardial effusion, signs of heart compression or masses (Figure 3).
    - Near Infrared Spectroscopy (NIRS) monitoring to assess any worsening of the SVCS-induced cerebral edema.

The sentence (Page 2, line 75) is grammatically unclear.

REPLY: We really thank the reviewer for pointing this out. The text now reads:

Line 242 - Poiseuille's law states that the flow resistance is directly proportional to the fourth power of the radius when the cross-section of the airway is reduced. In this case, post-stenotic turbulent flow is produced via positive pressure ventilation. Although air can overcome the stenotic airway due to the positive pressure, it cannot be completely flushed out during the expiratory phase due to the obstruction and the lack of laminar flow, which impede gas exchange and encourage the genesis of air trapping phenomena.

The word "sensibility (Pg 4, Line 139 should be changed to "sensitivity".

REPLY: We really thank the reviewer for pointing this out we corrected the misspelled word.

Overall, despite the above comments, I think that discussions of the merits of pre-emptive ECMO planning and or cannulation for high risk patients with mediastinal mass syndrome is a good thing for this population and therefore the manuscript deserves to be aired.

REPLY: We really thank the reviewer for her/his appreciation.

Reviewer D

I enjoyed reading the review and found it informative, thank you.

REPLY: We really thank the reviewer for her/his words of appreciation.

Here are some points to consider:

1) Although the phases of anesthetic care are covered in detail with supporting evidence, it is never made clear what the surgery is, or at least what approaches to resection of the tumor might affect management. For example, a simple biopsy would be a much different discussion than radical thoracic resection.

REPLY 1. We are very grateful to the reviewer for these comments.

We agree that anesthesiological planning varies according to the expected type of surgery. Our review is thought for tumour resection surgery, not for simple biopsy or minor surgery (e.g. procedures in local anaesthesia). Therefore, we decided to underline this aspect by modifying the text as follows:

Line 197 - The anesthesiologist's approach varies according to the type of planned surgical procedure. Therefore, our review aims to provides insight into the perioperative planning of patients undergoing major mediastinal surgery, leaving aside minor procedures.

2) A discussion of intraoperative management for "safe" would be helpful to better contrast with "unsafe" or "uncertain" patient populations.

REPLY 2. We fully agree with the reviewer's remak. We then decided to specify even the intraoperative and postoperative management for patients classified as "safe". The text was modified as follows:

Line 693 - The anesthetic approach should be tailored to the patient's risk class (*Table 1*) and the need for possible ECMO support. Patients classified as *safe* should receive the same care dedicated to major thoracic surgery. Nonetheless, as already pointed out, anesthesia induction and intrathoracic pressure changes may exacerbate a cardiorespiratory collapse even in asymptomatic patients.

3) Since the review focus on cardiopulmonary compromise and the use of ECMO, should that be explicitly stated in the review's title?

REPLY 3. We thank the reviewer for the suggestion. If the Editor agrees we may try to change the title to stress the importance of ECMO in this type of surgery. We modified the title as follows:

"The anesthetic management and the role of extracorporeal membrane oxygenation for giant mediastinal tumor surgery"

4) Please define "NIRS" and "EPS" block.

REPLY 4: We would like thank the reviewer for her/his comment. We modified the text as follows:

Near Infrared Spectroscopy (NIRS) monitoring to assess any worsening of the SVCS-induced cerebral edema.

And

The search for less invasive and safer techniques is then advocated. The erector spinae plane (ESP) block might be the regional anesthesia technique of choice for the patient. It carries a low-risk profile, far from the pleura, spinal cord, and major blood vessels [32]. It can be performed with high safety even in patients with impaired coagulation, and it demonstrated similar pain relief effects compared to thoracic paravertebral block [33]. In a randomized controlled trial conducted on sixty patients, ultrasound-guided ESP block exhibited a significant analgesic and opioid-sparing effect in patients undergoing thoracotomy surgery [34].