Peer Review File

Article information: https://dx.doi.org/10.21037/ccts-21- 33

Review Comments (Round 1)

Reviewer A

I would like to congratulate the authors for the comprehensive review on pulmonary hemodynamics and lung surgery. The authors provided a clear summary of the relevant pulmonary circulatory anatomy and physiology with emphasis on clinical relevance. The manuscript's language is clear, length is just right and figures are well-presented. Figure 3 is especially relevant for clinicians who evaluate individuals pre-operatively.

A few minor comments:

Comment 1:
Perhaps the flow of the manuscript could be improved by discussing the anatomy/physiology of pulmonary circulation, definition of right ventricular dysfunction and then followed by consideration in the pre-op assessment, operative concerns e.g. single lung ventilation/anesthesia and then effect of lung resection on right ventricular function.

Reply to Comment 1:
We thank the reviewer 1 for this comment. Actually, we decided to present the different section in a chronological order. In fact, we explain the anatomy, the physiology, the pre-op evaluation and after that the consequences that we may encounter during the operative period.

Comment 2:
While the product of total arterial compliance and PVR is often assumed or regarded as a constant, there is emerging evidence that this concept may be an oversimplification and that time constant may be variable in health and disease.

However, discussing further may be beyond the scope of this review.

Reply to Comment 2:

We agree with the comment related to the product of the total arterial compliance and PVR that can be variable according to various physiologic conditions including change in left atrial pressure for example. [1, 2] This omission was voluntary, not to oversimplify, but to keep the concept accessible to the reader that may not be familiar with these physiologic concepts. In order to take into account the physiologic states where it can change, revision to that sentence has been proposed.

Change in the text related to Reviewer A, Comment 2:

The relationship between capacitance or compliance and PVR follows a hyperbolic function, where the product of the two is a constant (τ = PAPc x PVR) that only show minimal changes in the context of disease or medical treatment

Comment 3:

The description on Belda et al 2018 study, 'fixed tidal volume of 5-6 mL/kg predicted body weight combined with a PEEP of 20 cmH2O' may be potentially misleading. Perhaps could consider '...a maximum PEEP of 20cmH2O followed by an individualized or titrated PEEP, led to reduced driving pressures...'.

Reply to Comment 3:

I thank the reviewer for that remark. The sentences were adapted to make it clearer.

Change in the text related to Reviewer A, Comment 3:

A recent prospective multicenter study showed that an open-lung approach during one-lung ventilation consisting of alveolar recruitment maneuvers, tidal volumes of 5 to 6 mL · kg^{-1} predicted body weight to maintain plateau pressure of 25 cm H_2O or lower, combined with a maximum PEEP of 20 cm H_2O follow by an individualized PEEP according to the highest dynamic compliance, led to reduced driving pressures and improved pulmonary outcomes.

Reviewer B

Thank you for submitting a valuable review manuscript for CCTS.

In the manuscript titled 'Pulmonary hemodynamics and lung surgery', the authors review various aspects of pulmonary hemodynamics during or after lung resection surgery. I totally agree that this review manuscript contains a lot of information that might be helpful to readers. However, as a reader who has always been interested in this topic, I felt perplexed when reading this manuscript, because too much information was presented sporadically, and not unified to reach conclusions.

Comment 1:

A review article is not a just collection of knowledge and should provide a comprehensive analysis of a specific topic. In my opinion, the main topic of this manuscript is 'hemodynamic change after lung resection'. If so, all the subtitles and content of the manuscript should target and arrange for that topic. However, I can hardly find the effect of lung resection in the aspect of 'right ventricular contractility', 'right ventricular afterload', 'static component of the right ventricular workload; pulmonary vascular resistance', and 'pulsatile and static component of the right ventricular workload: compliance, pulmonary artery: input impedance and effective arterial elastance'. Changes after lung resection should be added to the contents described under these subtitles. Only then, can readers understand the 'proposal functional evaluation prior to lung resection' in the section of 'Evaluation of the pre-operative hemodynamic status'.

In conclusion, as a reviewer, I do not think all the contents of this review manuscript are well-organized and unified to reach the topic 'pulmonary hemodynamic changes after lung surgery'.

Thank you for submitting this insightful and full-of-knowledge review manuscript.

Reply to Comment 1:

The main topic of this article is pulmonary hemodynamics and lung surgery as stated in the title. The orientation of the manuscript is aim to answer hemodynamic particularities related to lung surgery and not only lung resection. This is the reason why we talked about the effect of epidural analgesia and one-lung ventilation. The effect of lung resection on hemodynamics is explained

in the section “Effect of lung resection on right ventricular function”.

Reviewer C

We very much look forward to reading the next iteration of the manuscript.
Additional comments:

Comment 1:
Line 110: I think the authors are referring to the anteriomedial, or inside (concavity) of aortic arch.
Reply to Comment 1:
I thank the reviewer for that observation. Modification has been made to the sentence in order to reduce confusion.
Change in the text related to Reviewer C, Comment 1:
Right and left bronchial arteries ostia are generally located on the anteromedial and anterolateral aspect of the thoracic aorta. They provide oxygenated blood to the bronchial tree.

Comment 2:
Line 116: what are the superficial and deep bronchial veins, and what is the rationale for distinguishing them? Perhaps a Figure would be helpful to illustrate the authors’ point?
Reply to Comment 2:
We agree with you, there is not point to distinguish these two systems that are not well explained in the literature. The sentence has been modified accordingly.
Change in the text related to Reviewer C, Comment 2:
Most of the bronchial arteriolar blood drains into the bronchial venous system which drains into pulmonary veins. Bronchial vein located around segmental and subsegmental bronchi will empty in the azygos and hemiazygos systems. [3]

Comment 3:
Line 128 (now 127): We are not sure what is meant by physiologic constellation.
Reply to Comment 3:

The constellation refers to the high compliance of the pulmonary arterial system and the low vascular resistance of the pulmonary arterial system. Matched together (high compliance, low resistance) explains why the right ventricle can accommodate volume and works best under low afterload (low pulmonary arterial resistance). Clarification has been made to that sentence.

Change in the text related to Reviewer C, Comment 3:

The high compliance and low vascular resistance of the pulmonary arterial system explains how the right ventricle is capable to accommodate volume (preload) and performs best under low afterload conditions.

Comment 4:

Paragraph line 135: This discussion is very detailed. Is it all relevant? Can this paragraph be condensed?

Reply to Comment 4:

This comment refers to the paragraph related to right ventricular dysfunction. I think it is important to give that information to the reader in order understand the fact that right ventricular dysfunction and failure is not uniformly defined in the literature and that multiple definitions exist.

Change in the text related to Reviewer C, Comment 4:

The two last sentence of the paragraph has been removed because they are not directly related to lung resection surgery.

Comment 5:

Line 157: The authors mention the expected reduction in RV ejection fraction following lung resection; could they specify the extent of lung resection that is referred to here (as the effects of a wedge resection, for instance, would likely not be comparable to a lobectomy)?

Reply to Comment 5:

This is a good remark. Unfortunately, we do not have a clear and definite answer to that question. Studies addressing the question of reduction in right ventricular function after lung resection generally pooled every lung resection (segmentectomy, lobectomy, pneumonectomy) together to one single population and does not provide reduction in RV ejection fraction (RVEF) according to

extend of lung resection for example. It makes sense to hypothesize that the larger the resection, the larger the reduction in compliance with subsequent proportional reduction in RVEF due to increase RV afterload. This hypothesis is stated in the last sentence of the third paragraph of that section. Despite being a hypothesis, this has not been addressed very well in the cited literature. Most of the patients in the studies are having lobectomy and pneumonectomy and very few are having segmentectomy.

The only study that compared reduction in RVEF between pneumonectomy and lobectomy is from Elrakhawy et al. They reported various hemodynamic findings from a pulmonary artery catheter capable of providing RVEF. They reported that RVEF reduction was greater after pneumonectomy compared to lobectomy.
Reference: Elrakhawy HM, Alassal MA, Shaalan AM, Awad AA, Sayed S, Saffan MM. Impact of Major Pulmonary Resections on Right Ventricular Function: Early Postoperative Changes. Heart Surg Forum. 2018;21(1):E009-E17.

Even though we do not have abundance of literature to support a proportional reduction in RVEF in accordance with the extension of lung resection, we think the focus should be placed on the fact that patient who experienced a larger degree of RV dysfunction are at risk of more complications.

Comment 6:
Line 172: Could the authors explicitly describe « right ventricular end-diastolic volume index » for the benefit of non-physiologists who will be reading the paper?
Reply to Comment 6:
This refers to the right ventricular end-diastolic volume over body surface area.
Change in the text related to Reviewer C, Comment 6:
The term “right ventricular end-diastolic volume index” has been removed to reduce confusion and ease reading.

Comment 7:
Lines 188-192: The authors cite literature that suggests VATS would have less of

an effect on right heart hemodynamics than open surgery. Given an equal extent of lung resection, this is not necessarily intuitive. Is there- any underlying rationale that the authors can provide or suggest?

Reply to Comment 7:

That is a good question. It is thought that the larger reduction in right ventricular function after a thoracotomy compared to a VATS could be related to the extent of manipulation and chest damage. This has been added to the manuscript.

Change in the text related to Reviewer C, Comment 7:

In fact, it is thought that the larger damage to the chest wall, the amount of surgical manipulations in addition to the extent of lung resection could explain the larger increase in pulmonary vascular resistance after a thoracotomy leading to reduced right ventricular performance.

Comment 8:

In the section on right ventricular contractility, on lines 209-210, the authors mention how one assesses ventriculo-arterial decoupling. What are the clinical implications of this?

Reply to Comment 8:

I think it is important to understand what the goal standard of right ventricular systolic function assessment is. It has been presented in a manner to draw differences with the left ventricular function. This might help the reader understand the particularity of the right ventricle. It is difficult to find clinical data to match this concept with lung surgery as the use of conductance catheter is almost never used in clinical setting.

Comment 9:

Line 247: The term « proximal reflectors » may not be understood by everyone. Perhaps the authors could elaborate and describe the mechanism of what is going on here.

Reply to Comment 9:

We added more explanation to help the reader understand the idea.

Change in the text related to Reviewer C, Comment 9:

This ratio can increase to higher than 1.0 in circumstances of increased pulsatility such as in chronic thromboembolic pulmonary hypertension due to increase in systolic pulmonary artery pressure from strong proximal reflection. Pressure wave reflection occur at arterial branch point, arterial branch point and at sites of change in vessel caliber. Normally these pressure waves are attenuated by compliance of arterial vessels. However, pulmonary artery diseases modify vessels by increasing their stiffness and reducing their compliance explaining the large PAPpp/PAPm ratio.

Comment 10:

Line 304-5: Can the authors elaborate on the conceptual differences between the Revised Cardiac Risk Index and the Thoracic – RCRI?

Reply to Comment 10:

In order to answer to that comment, we added the components of the original RCRI and a sentence to explain the difference between the original RCRI and the Thoracic-RCRI.

Change in the text related to Reviewer C, Comment 10:

Revised Cardiac Risk Index (RCRI) incorporate 6 risk factors to predict major cardiac complication after major noncardiac surgery; (1) high-risk surgery, (2) history of ischemic heart disease, (3) history of heart failure, (4) history of cerebrovascular disease, (5) diabetes mellitus treated with insulin and (6) preoperative serum creatinine > 2.0 mg/dL. (42) RCRI considers patient factors more than the risk of the operation. (…) In fact, the Thoracic-RCRI has removed the presence of heart failure and high-risk surgery from the original RCRI. It also reduced the weight of the preoperative serum creatinine > 2.0 mg/dL in the risk calculation.

Comment 11:

Line 321: The authors mention « right ventricular peak longitudinal strain of the right ventricular lateral wall »; can the authors elaborate on what this refers to, both conceptually and in practice? Perhaps with a figure?

Reply to Comment 11:

We agree that this echocardiographic parameter of ventricular systolic function

is not as common as the ejection fraction. We added a sentence to give more insight to the reader about the pertinence or the benefit of the later in the context of thoracic surgery.

Change in the text related to Reviewer C, Comment 11:

This metric is a marker of mechanical deformation of the ventricle and has been proved to be very sensitive to detect changes in systolic function before reduction in ejection fraction is various pathological states. (51)

Comment 12:

Lines 321-324: Can the authors relate the RV changes noted after lung resection and potentially lasting several weeks, to the theoretical concepts that they discuss beforehand?

Reply to Comment 12:

We decided to present theoretical concept related to the right ventricle & pulmonary artery unit in order to give the reader a physiologic view of the pulmonary hemodynamics. It is difficult to make translation between these physiologic concept and right ventricular effect of lung resection.

Change in the text related to Reviewer C, Comment 12:

Nevertheless, we added the following sentence the reflect the absence of literature regarding the consequences of this specific decrease in right ventricular function after lung surgery: “The clinical impact of these specific long-lasting changes in right ventricular function are not know.”

Comment 13:

When discussing exercise tolerance of patients (VO2-max), how is this related to right heart function?

Reply to Comment 13:

Evaluation of VO2-max is an important part of the preoperative cardiovascular evaluation and should be included in such evaluation to have a better idea of the surgical risk of the patient. It has been shown that right ventricular function assessed using strain measurement correlates with VO2-max and VE/VCO2 in a population of patient having pulmonary arterial hypertension but not in patient with chronic thromboembolic pulmonary hypertension. This might be due to the

presence of ventilation - perfusion mismatch in the latter population. We do not have literature regarding this association in preoperative thoracic surgery patients. This is the reason why I did not comment on the relation between RV function and VO2-max in the manuscript.

Ref: Rehman MB, Howard LS, Christiaens LP, Gill D, Gibbs JSR and Nihoyannopoulos P. Resting right ventricular function is associated with exercise performance in PAH, but not in CTEPH. Eur Heart J Cardiovasc Imaging. 2018;19:185-192.

Comment 14:

In the section on right ventricular hemodynamics and one lung ventilation, the authors discuss the possible effect of oxygen fraction, but there is no direct discussion of how this is relevant to lung surgery and anesthesia. What are some of the practical implications and take-aways?

Reply to Comment 14:

The first sentence of this section has been modified in order to reflect the anesthesia consideration of managing oxygen fraction in order to reduce the risk of hypoxemia that could increase pulmonary artery pressure and consequently, induce right ventricular dysfunction.

Change in the text related to Reviewer C, Comment 14:

Anesthesia management during one-lung ventilation should be adapted to reduce incidence of hypoventilation and hypoxemia. This should be done to decrease the risk of pulmonary hypertension and consequently, right ventricular dysfunction that could produce systemic complication from high venous pressure such as bleeding and acute kidney injury for example.

Comment 15:

In their discussion on RV dynamics and single-lung ventilation, could the authors mention what implications this would have on intraoperative about RV/hemodynamic monitoring intra-op?

Reply to Comment 15:

Monitoring and right ventricular function is a very broad topic. We think that the main concerns related to right ventricular function and the perioperative

surgical risk has to be address prior to surgery in order to propose the best therapeutic plan to the patient. Right ventricular monitoring can be achieved through hemodynamic monitoring using central venous catheter or pulmonary artery catheter, but this is not routinely used in lung resection surgery. Right ventricular monitoring can also be done using transesophageal echocardiography in selected patients, but the clinician must keep in mind the possible difficulties related to position of the patient and the risk of trauma to structure of the oro-phageal carrefour.

Change in the text related to Reviewer C, Comment 15:

Advanced hemodynamic monitoring can be done using pulmonary artery catheter or transesophageal echocardiography in selected patient at risk of developing right ventricular dysfunction secondary to pulmonary hypertension during one-lung ventilation. When using transesophageal echocardiography, the clinician must keep in mind the possible difficulties related to position of the patient and the risk of trauma to structure of the oro-phageal carrefour.

Review Comments (Round 2)

Reviewer A

We thank the authors for the work they put into revising the mansucript.

The structure of the text has been improved. As a general comment, I would say that the theorectical section remains somewhat too long and some of the theoretical concepts are quite complex, and their practical relevance, if any, often does not clearly stand out in the text. There is also quite an abrupt separation between the theoretical section and the latter section of the paper where practical concepts are discussed. Practical considerations are often not clearly related to the theoretical concepts presented earlier.

Overall, I think the manuscript still requires significant improvement before it can be considered for publication. I expect it may take a couple of iterations before we get there, but we will gladly accompany the authors throughout this

process.

Below are some specific comments to help guide the authors in their revisions.

Comment 1: In paragraph lines 83-87, the authors lay out the structure and objectives of the paper and make it clear that the focus is on right heart function and pulmonary hemodynamics as they relate to pulmonary surgery. The authors should insure that the ensuing text is consistent with these objectives.

Reply to Comment 1: We thank the reviewer for these comments. We deeply reviewed and reorganized the manuscript. In fact, we reframed the anatomic & physiologic section to keep the most important message and concepts. We also reframed the middle section to put more emphasis on the different factor that can affect the right ventricular function during lung resection surgery. Consequently, we reformulated the last paragraph of the introduction.

** Please note that the mentioned lines in this document may not correspond to the lines in the last version of the reviewed manuscript due to edition.*

*** Please also note that the original figure 2 (graph of pulmonary artery compliance and pulmonary vascular resistance) has been removed and the figure 3 has been renamed "Figure 2" to respect continuous numerical order.*

Change in the text based on Comment 1:

(Line 150) This review will discuss anatomic and physiologic considerations the pulmonary artery unit. Intraoperative factors affecting the right ventricular function will presented including. The impacts on right ventricular function of lung resection, surgical approach, epidural analgesia, fluid therapy and one-lung ventilation will be explored. Finally, the role of pre-operative hemodynamic and functional evaluation will be examined with a focus on risk stratification. The following article is presented in accordance with the narrative review reporting checklist.

** As it would create redundancy to copy-paste all the modifications related to this comment, we refer the reviewers to the manuscript itself.*

Comment 2: Regarding the bronchial circulation, are there any practical considerations (documented or potential), for example on the extent of lymph

node dissection, fluid balance, and pulmonary hemodynamics? (for example, extensive lymph node dissection is a documented risk factor for post-pneumonectomy ARDS).

Reply to Comment 2: The clinical impact of bronchial circulation has been explored in the field of lung transplantation. A sentence has been added to the paragraph to give the reader a clinical perspective related to bronchial arterial system. I tried to stay limited regarding this very specific subject (bronchial artery revascularization in lung transplant) because it goes a little far from right ventricular function and lung resection. I did not address post-pneumonectomy risk factor as it is not directly related to right ventricular hemodynamics. This topic could be the subject of an entire article.

Change in the text based on Comment 2: (Line 184) Bronchial arteries are scarified and ignored during the lung transplantation process. This led to persistent hypoxia in the transplanted lung, which may be the cause of chronic allograft dysfunction.

Comment 3: Lines 135-138 (now line 223): the authors list a series of factors affecting pulmonary vascular resistance; how do these factors come into play during or after lung surgery?

Reply to Comment 3: Hypoxia, hypercarbia & respiratory acidosis and high airway pressures came into play during one-lung ventilation and has been address in this section of the manuscript. High hematocrit may be related to hypovolemia and has been named in the section regarding the pulmonary vascular resistance in the small vessels. Anatomic factors such as pulmonary emboli, primary pulmonary hypertension, or left heart conditions such as mitral valve stenosis or regurgitation, and systolic or diastolic left ventricular dysfunction has been addressed in either the part of the manuscript tackling surgical aspect or the one related to pre-operative cardiopulmonary evaluation. These factors are very well known in the anesthesiology literature to be potential pulmonary hypertension inducer or contributor.

Comment 4: Line 140 (now line 278): « Effects of lung resection on right ventricular function » : The first couple of paragraphs of this section are critical.

How does the extent of lung resection affect RV parameters and RV function? Are these effects evident during or after surgery? Could the authors clearly distinguish intraoperative and postoperative effects and considerations? This would obviously also have implications regarding intraoperative monitoring and management.

Reply to Comment 4: I added a section to explain a few concepts related to hemodynamic monitoring that directly apply to thoracic surgery, especially lung resection surgery. As we very rarely monitor right ventricle (using a pulmonary artery catheter or transesophageal echocardiography) during lung resection surgery, it is not possible to define the very exact moment where these changes occur. To answer your question "Are these effects evident during or after surgery?" we do not monitor enough right ventricular function during the lung resection surgery to observe these changes. Clear distinctions have been made regarding the fact that pneumonectomy induced significantly more change in right ventricular function compared to lobectomy (section starting at line 278).

Comment 5: Paragraph line 163 (now line 194 to 221): This is a critical paragraph. What explains the increases in pulmonary vascular resistance during or after surgery? How is it related to « reduced lung compliance »? Are we talking about reduced « lung » compliance or reduced vascular compliance here, or both, as they are interrelated? The reader will have some intuitive understanding of what the authors are trying to convey but all these details are highly important and need to be explicitly stated.

Once gain, I think it is very important to clearly lay out factors that affect intraoperative hemodynamics and distinguish them from what affects post-op hemodynamics.

Reply to Comment 5: This section related to pulmonary vascular resistance has been reformulated and moved in the "Physiology of the pulmonary vascular unit". Clarifications have been added to specify lung and vascular parenchyma throughout the manuscript. Please refer to the line 194 to 221 of the revised manuscript).

Comment 6: Line 204 (now line 318); How would larger damage to the chest

wall affect right heart hemodynamics?

Reply to Comment 6: Larger damage to the chest wall by extensive surgical incision are associated with more important lung parenchymal manipulation and resection. In fact, better right ventricular hemodynamic results from VATS compared to open thoracotomy. Also, the literature seems to point in the same direction with study reporting that 24 h after surgery, lung cancer patients that underwent VATS had higher right ventricular ejection fraction, cardiac and stroke volume index compared to thoracotomy patients.

Comment 7: The sections line 220, 238, 247, 264, 323 introduce several very complex theoretical concepts related to the function of the RV and the pulmonary circulation. The authors also include several equations to illustrate how these variables are measured and calculated. These sections are difficult to follow and the theorectical concepts are not discussed in a practical context or from a perspective of clinical relevance. In fact, several of these concepts are not mentioned at all in the ensuing text. The authors should rethink the concepts they choose to include; I think that a good litmus test would be to consider whether they have any relevance to preoperative evaluation, intraoperative management, and postoperative outcomes.

Not only should the authors endeavour to relate theory to practice as far as intraoperative and postoperative conditions, but also as to the degree that these concepts are relevant in the context of frequent thoracic surgery patient comorbidities such as COPD, pulmonary fibrosis, etc.

Reply to Comment 7: I have made significant modifications to that section of the manuscript. I still believe that physiologic concept of right ventricular contractility, afterload and right ventricular to pulmonary artery coupling are critical concept to be understood by anyone working in the field of thoracic anesthesiology. The importance of the right ventricular adaptability to its afterload is a key concept in the field of pulmonary hypertension and right ventricular dysfunction as consequences of these two diseases happen when the right ventricle became uncoupled to its afterload and its adaptative mechanism got overpass.

I removed figure 2 but kept figure 1 as I believe the reader should have visual

access to these key concepts. As they may go beyond the scope of this review, they are not developed in the main body of the manuscript.
(Reference: Vonk Noordegraaf A, Westerhof BE and Westerhof N. The Relationship Between the Right Ventricle and its Load in Pulmonary Hypertension. J Am Coll Cardiol 2017; 69: 236-243. DOI: 10.1016/j.jacc.2016.10.047.)

Comment 8: The discussion of pulmonary function testing (line 362) is unrelated to the entire previous discussion on right heart hemodynamics. Thoracic surgeons are generally familiar with pulmonary function tests, but it would be very interesting if the authors could relate such testing to right heart function.
Reply to Comment 8: In fact, the section addressing pulmonary function testing has been removed. Figure 3 has been kept and placed accordingly in the section regarding cardiopulmonary stress testing (now Figure 2).

Comment 9: Section line 400 (now line 389): « Right ventricular hemodynamics and one-lung ventilation ». This section begins to explore ideas that the reader has been waiting for. Still, sometimes the flow of the text is a bit difficult to follow and some concepts are introduced that are purely relevant to one-lung ventilation as it pertains to the lung, rather than the RV. It would be helpful if the authors could elaborate further on the ideas that are discussed in this section.
Reply to Comment 9: We addressed the effect of one-lung ventilation on right ventricle. We explained the effect of hypoxia, hypercapnia, atelectasis (lost in functional residual capacity) on pulmonary vascular resistance and right ventricular function. We finally report a ventilation strategy to protect right ventricle with notice regarding one and two lung ventilation.
** As it would create redundancy to copy-paste all the modifications related to this comment, we refer the reviewers to the manuscript itself.*

Comment 10: Improving English-language syntax will improve clarity, and I suggest English-language proof-reading.
Done

Reviewer B

With regard to Reviewer C in Round 1, Reply to comment 7：

The authors cite literature that suggests VATS would have less of an effect on right heart hemodynamics than open surgery. The reason given by the author lacks evidence. It would be better if the authors clarify in the article that there is currently no sufficient evidence to prove this speculation, or this part of the content should be deleted.

Further Reply to Reviewer C, Reply to comment 7:

There are 2 studies regarding the impact of surgical approach (VATS versus open thoracotomy) on right ventricular function. Both studies have been done by the same group of Dr Mikami and Dr Yamagishi from department of surgery, division of thoracic surgery, Nippon Medical School in Tokyo, Japan. These 2 studies are small and have important methodological limitation, but they are the only citable reference to answer that question. I added nuance and explanation on interpretation of results findings.

Change in the text based on Reviewer C, comment 7:

The paragraph now reads: “Despite the benefits of VATS over thoracotomy, the effect of the surgical approach on the post-operative right ventricular function is not so clear. A first study by Mikami et al. showed that 24 hours after surgery, lung cancer patients that underwent VATS had higher right ventricular ejection fraction, cardiac and stroke volume index compared to thoracotomy patients. In fact, it is thought that the larger damage to the chest wall by extensive surgical incision, the amount of surgical manipulations in addition to the extent of lung resection could explain the larger increase in pulmonary vascular resistance after a thoracotomy leading to reduced right ventricular performance. This suggests that the VATS approach might be protective and allow for a compensatory hyperdynamic phase in the first postoperative day which could contribute to a faster recovery from the intervention. However, their results were not replicated by Yamagishi et al. In fact, this group compared VATS with muscle-sparing thoracotomy and found that at 36 hours perioperatively, the VATS group had a greater reduction in the mean pulmonary artery pressure,

pulmonary capillary wedge pressure and total pulmonary resistance index compared to the thoracotomy group. Despite this benefit in term of afterload reduction, there were no significant differences between the two groups in right ventricular performance assessed by continuous cardiac output monitoring system from pulmonary artery catheter. It is difficult to draw definitive conclusion from these small studies. Right ventricular performance is affected by the extend of lung resection. Thus, it can be assumed that extensive lung resection will be associated with more lung parenchymal injury and pulmonary vasospasm from surgical interventions leading to more pronounced hemodynamic variation. These changes in pulmonary vascular resistance and right ventricular performance are more related to the extent of lung resection instead of the inherent surgical approach chosen to perform lung resection."

References related to that comment:

Mikami I, Koizumi K and Tanaka S. Changes in right ventricular performance in elderly patients who underwent lobectomy using video-assisted thoracic surgery for primary lung cancer. Jpn J Thorac Cardiovasc Surg 2001; 49: 153-159. 2001/04/18. DOI: 10.1007/BF02913593.

Yamagishi S, Koizumi K and Shimizu K. Assessment of the perioperative hemodynamics and right ventricular performance of lung cancer patients using a continuous cardiac output monitoring system: comparison between video-assisted thoracic surgery and muscle-sparing thoracotomy. Ann Thorac Cardiovasc Surg 2006; 12: 166-173. 2006/07/11.