PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Does primary posterior tracheopexy prevent collapse of the trachea in newborns with oesophageal atresia and tracheomalacia? A study protocol for an international, multicentre randomised controlled trial (PORTRAIT trial)

Authors

van Stigt, Marit; van Hal, Anne-Fleur R.L.; Bittermann, Arnold J.N.; Butler, Colin R.; Ceelie, Ilse; Cianci, D.; de Coppi, Paolo; Gahm, Caroline; Hut, Julia; Joosten, K; Lemmers, Petra M.A.; Mullassery, Dhanya; Nandi, Reema; Pullens, Bas; Staals , Lonneke; Svensson, Jan F.; Tytgat, Stefaan H.A.J.; van de Ven, Peter M.; Wijnen, Rene M.H.; Vlot, John; Lindeboom, Maud Y.A.

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Obeida, Alaa**
Affiliation surgery	**Yorkshire and the Humber Postgraduate Deanery, General**
Date	**02-Jun-2024**
COI	**No competing interests.**

This is an important trial that should change the surgical approach for cases of OA associated with TM. The trial is well-structured and a clear pathway is described. An objective assessment method is clearly described and this is a good addition to the symptomatic assessment of TM.

I got few comments, though.

- I think you need to highlight more why you are doing posterior tracheopexy rather than aortopexy as a selected intervention.

- During the pre-operative TBS, if a case with severe TM is detected, would you still proceed with randomization? Would you consider performing the tracheopexy as a treatment modality? Will the parents be aware during consenting that even if severe TM is detected, you will still proceed with randomization?

- It is not mentioned that during TBS assessment you will look for blood vessel compression as a cause of TM which would be more favourable to perform aortopexy for such cases.

- Will only cases with flaccid posterior membrane of the trachea have the posterior tracheopexy OR all cases with TM regardless of the location of weakness or vascular compression?

Reviewer **2**

Name **Zendejas, Benjamin**

Affiliation **Boston Children's Hospital Department of Surgery**

Date **02-Jun-2024**

COI **None, other than I am biased and a firm believer in primary posterior trachepexy.**

Overall, I am very pleased to see this trial getting underway. Congrats on this effort. It will be a huge leap forward and it is very much needed. My comments below are meant to strengthen the relevance of this study and the impact on the care of these children. I want you to succeed with this study hence please take my recommendations seriously.

Page1, Row 28-35= I somewhat disagree with this paragraph. The reason why TBM is so prevalent in this population relates to a field defect, EA/TEF affects both the esophagus and the airway. Particularly type C defects which have a fistula to the airway, the airway at the location of the TEF has a much wider posterior membrane and hence the cartilage to membrane ratio is abnormal, this wide membrane leads to instability and excess collapse. I do not think TBM is caused by the initial EA repair, though it can be exacerbated if there is a poor technique for TEF closure (leaving a large diverticulum), but rather we should assume all children with EA/TEF are at risk for TBM given to the underlying field defect that occurs in the esophagus/airway. Furthermore, by fixing the esophagus via the right chest, we naturally leave the esophagus siting right behind the trachea, if you add an esophageal stricture to the picture, the proximal or upper esophagus distends and worsens the TBM. Somewhat of a vicious circle.

Page2, Row 27-36..Not sure I agree with you. Evaluation of tracheal collapse/diameter is a subjective measure, prone to rater bias. It has been done before. Need to be specific if assessing shallow breathing or active cough. There are some “hard” symptoms that patients can present with such as blue spells requiring CPR or hospitalizations requiring oxygen or ICU admissions secondary to severe respiratory infections. I would suggest you not rely exclusively on the % collapse as your primary measure. I believe a more clinically relevant outcome measure such as reduction/elimitation of blue spells in the first year of life would be more clinically relevant/meaningful. We have data to show that approximately 20% of

children with EA/TEF experience a blue spell in the first year of life if they don't undergo a primary tracheopexy.

I profoundly disagree with your inclusion criteria of only randomizing those with collapse. The problem is your definition. What % will you consider severe enough to consider TBM. We well know that most of the time its not that obvious when they are newborns. Its also not customary for most surgeons to do a proper 3 phase dynamic bronchoscopy in a child with an active fistula as most surgeons and anesthesiologist are more worried about the active fistula and hence won't spend the appropriate time to perform an accurate diagnosis. Also, many times a child may be deemed as not having TBM preoperatively, and only to develop severe TBM shortly after repair. It is not reliable to base your diagnosis on preoperative bronchoscopy. I strongly believe you should include all newborns with type C, EA/TEF regardless of their initial bronchoscopy. This way you will have much less variability/surgeon bias/selection bias on the inclusion of patients. You can later stratify based on certain % collapse but I bet you that unless you have a central monitoring review of each preoperative bronchoscopy video (which you may want to consider anyway) you will not have a way to reliably diagnosis TBM pre-repair.

For exclusion criteria why base it on gestational age? Why not weight instead? I'd say there are many kids who are 32-33 weekers with good weight who are good candidates. Maybe just limit it to <2kg or whatever you don't feel comfortable with. Also there is a flexible bronchoscope that is 2.2mm diameter so it can fit via a 2.5ETT, so not sure about your size 3 ETT exclusion criteria.

The other reason to avoid fixating on % collapse pre- to post-op is that we know that % collapse does not always correlate with symptomatology. Most of the time it does but not always. We have children who have great looking airways with no significant collapse and can have respiratory symptoms. While others can have significant collapse but no major symptoms. Key is to measure both but not get too fixated on % collapse. Symptoms are more important! One more reason to not fixate on % collapse is that you are forcing or exposing children to a second anesthetic just to measure their % collapse. What if they are not having symptoms? Would you still expose them to an anesthetic? I would not. Focus on symptoms!

One of the technical things we have learned with doing several primary PTs is to place the pexy sutures (which by the way we recommend them being pledgeted with autologous tissue – pleura or azygous vein, and horizontal mattress) on the airway and spine but not tie them down until you have completed your esophageal dissection and ideally anastomosis (if you are doing it via thoracotomy), this way it makes the esophageal anastomosis easier and you are not tugging or pulling on a airway that is pexied to the spine as it can tear in a small delicate airway of a newborn. Yes, for a thoracoscopic anastomosis, it would be in the way so in that case yes the airway pexy goes before the anastomosis but only after you have completed your proximal esophageal pouch dissection.

How will you ensure competency/equivalent surgical technique of these surgeons doing these primary tracheopexies in all these centers? How many have each of them done? Any training intervention? Monitoring of technique via video? Teleproctoring/mentoring?

Please specify if your bronchoscopies will be rigid (with or without ventilating scope) or flexible. Ideally, need to keep them consistent. You may also want to standardize how the TEF is repaired (clips vs excision/fistulectomy vs simple ligation) – all of these can affect the risk of postop TBM..

For complications I would strongly encourage you to assess vocal fold movement impairment. This is a highly underappreciated form of respiratory morbidity for these children and at such high risk for injury during EA repair (some data say that up to 1 in 4 children can present with VFMI after EA repair). This mean all children would need a preoperative assessment of vocal fold motion (as some can be born with congenital VFMI), and postoperative assessments as well. All being non-sedated with flexible nasolaryngoscopy or with ultrasound if you have experience with laryngeal ultrasound as it has been shown to be reliable/accurate as well.

A few other things. Would suggest you monitor symptoms not just for first 6 months but for first year to capture the true burden in the first year of life as it has been captured in other studies in order to compare things better. Also, would suggest you evaluate feeding scores in these children (such as mFOIS), as some of these kids with really bad airways from TBM struggle to eat. Also as secondary endpoints don't forget about how many got tracheostomies for severe TBM or other entities.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1
Dr. Alaa Obeida, Yorkshire and the Humber Postgraduate Deanery, Cairo University Kasr Alainy Faculty of Medicine

Comments to the Author:
This is an important trial that should change the surgical approach for cases of OA associated with TM. The trial is well-structured and a clear pathway is described. An objective assessment method is clearly described and this is a good addition to the symptomatic assessment of TM.

Response: We would like to thank the reviewer for the evaluation of the manuscript and the compliments.

Comments:
1. I think you need to highlight more why you are doing posterior tracheopexy rather than aortopexy as a selected intervention.

Response: While in theory, an aortopexy is the preferred method to treat anterior TM, and a posterior tracheopexy (PT) the preferred method to treat posterior TM, most patients suffer from a combined anterior (wide, U-shaped cartilage rings) and posterior (flaccid post membrane) TM. There is no evidence regarding superiority of aortopexy or tracheopexy. Moreover, in some centres, a posterior tracheopexy is the preferred primary treatment option, with the option to perform adjunctively to a PT (1).

Most importantly, the posterior tracheopexy can be performed concurrently with the OA repair, and does not require a second intervention or a second approach. However, an aortopexy, would involve a second major surgery (including additional surgical incisions).

Since an aortopexy would therefore be more invasive compared to a posterior tracheopexy, we believe the PPT is more appropriate to select as intervention. We agree with the reviewer that should be highlighted more, therefore we have added the following sentences in the introduction section page 4, line 68-74:

"Surgical treatment options include anterior or posterolateral aortopexy and/or anterior or posterior tracheopexy (17,18). If the primary cause of the malacia is thought to be a flaccid posterior wall of the trachea, then a (secondary) posterior tracheopexy (PT) may be most indicated (19-22). If the primary cause is anterior TM, an aortopexy may be the preferred treatment approach (22). However, most patients suffer from a combined anterior (i.e. U-shaped tracheal rings, anterior compression) and posterior (i.e. flaccid posterior membrane) TM. Neither aortopexy or tracheopexy have been proven superior in the treatment of these combined TM patients (18,22)."

2. During the pre-operative TBS, if a case with severe TM is detected, would you still proceed with randomization? Would you consider performing the tracheopexy as a treatment modality? Will the parents be aware during consenting that even if severe TM is detected, you will still proceed with randomization?

Response: The superiority of the PPT has not yet been proven, even in patients with severe TM, as the severity of tracheal collapse does not always correlate with the development or severity of respiratory complaints. Moreover, this will be the first prospective study comparing the PPT to the wait-and-see policy. Therefore, there is equipoise between the two treatment arms (PPT vs no-PPT). Randomisation to either PPT or no-PPT is therefore justified, even for children with severe TM. During the informed consent meeting, parents or caretakers are notified of the randomisation process and the two possible treatment options. They will also be informed about the blinding to the randomisation group.

3. It is not mentioned that during TBS assessment you will look for blood vessel compression as a cause of TM which would be more favourable to perform aortopexy for such cases.

Response: During the preoperative TBS, all airway anomalies will be assessed, such as laryngeal clefts and vascular compression. The reviewer has brought to our attention that indeed we have not specified that only patients with primary TM will be included. Patients with pure secondary TM (for instance due to vascular compression) will not be included. In these patients, a CT-scan of the chest should be performed before treatment of the malacia can be carried out, which is standard of care and not part of this study protocol.

Therefore, we have altered this specific paragraph of the methods section on page 5 line 109-114, to the following:

"The severity of TM, as well as all other airway anomalies such as clefts and vascular rings, will be routinely assessed during the preoperative tracheobronchoscopy (TBS) prior to the OA correction. When primary TM is seen during this TBS, the patient will be included and randomised in either the PPT-group or no-PPT-group. When no primary TM is seen during the preoperative TBS, the patient will be excluded from the study prior to randomisation, and routine treatment is carried out."

4. Will only cases with flaccid posterior membrane of the trachea have the posterior tracheopexy OR all cases with TM regardless of the location of weakness or vascular compression?

Response: As addressed in the first and third question, primary TM is almost always a combination of anterior U-shaped tracheal rings, and a flaccid posterior membrane. All these primary TM patients will be included in this trial. Patients without primary TM (for instance, secondary TM caused by vascular compression) will be excluded from the trial, prior to randomisation, and routine treatment is carried out.

Reviewer 2
Dr. Benjamin Zendejas, Boston Children's Hospital Department of Surgery

Comments to the Author:
Overall, I am very pleased to see this trial getting underway. Congrats on this effort. It will be a huge leap forward and it is very much needed. My comments below are meant to strengthen the relevance of this study and the impact on the care of these children. I want you to succeed with this study hence please take my recommendations seriously.

Response: We would like to thank the reviewer for careful appraisal of the manuscript, and for the positive response on the efforts for this trial.

Comments:

1. Page1, Row 28-35= I somewhat disagree with this paragraph. The reason why TBM is so prevalent in this population relates to a field defect, EA/TEF affects both the esophagus and the airway. Particularly type C defects which have a fistula to the airway, the airway at the location of the TEF has a much wider posterior membrane and hence the cartilage to membrane ratio is abnormal, this wide membrane leads to instability and excess collapse. I do not think TBM is caused by the initial EA repair, though it can be exacerbated if there is a poor technique for TEF closure (leaving a large diverticulum), but rather we should assume all children with EA/TEF are at risk for TBM given to the underlying field defect that occurs in the esophagus/airway. Furthermore, by fixing the esophagus via the right chest, we naturally leave the esophagus siting right behind the trachea, if you add an esophageal stricture to the picture, the proximal or upper esophagus distends and worsens the TBM. Somewhat of a vicious circle.

Response: We expect this corresponds with Introduction section, page 3, line 59-63 of the marked copy. As suggested by the reviewer, we added the following sentences to discuss the above: "The cause of TM in OA patients is most likely multifactorial. Due to the presence of TOF, patients often have a wider posterior membrane leading to instability and collapse. Additionally, the tracheal rings in these patients are often U-shaped instead of the regular C-shape, resulting in a flatter trachea and increased collapsibility (2). Furthermore, following the surgical correction of OA and closure of the TOF, TM may be exacerbated."

The exact origin of TM in OA patients remains a topic of discussion, and will most likely vary between patients. We aim to investigate the role of the primary correction in this matter as a secondary objective, by comparing the preoperative TBS to the intraoperative TBS (after dissection of the surrounding tissues).

2. Page2, Row 27-36. Not sure I agree with you. Evaluation of tracheal collapse/diameter is a subjective measure, prone to rater bias. It has been done before. Need to be specific if assessing shallow breathing or active cough. There are some "hard" symptoms that patients can present with such as blue spells requiring CPR or hospitalizations requiring oxygen or ICU admissions secondary to severe respiratory infections. I would suggest you not rely exclusively on the % collapse as your primary measure. I believe a more clinically relevant outcome measure such as reduction/elimitation of blue spells in the first year of life would be more clinically relevant/meaningful. We have data to show that approximately 20% of children with EA/TEF experience a blue spell in the first year of life if they don't undergo a primary tracheopexy.

Response: We agree with the reviewer that symptoms and complications are a very important outcome measure to assess the efficacy and safety of the PPT. Therefore, we have included these as secondary outcomes. All of the symptoms described above will be recorded. However, we believe that performing an RCT based on clinical symptoms as primary outcome will not be feasible in neonates with OA, since respiratory symptoms, such as respiratory tract infections, are usually difficult to diagnose in babies. Additionally, postoperative symptoms are subjective to parental perception, and may therefore result a misrepresentation of patient outcomes. We have mentioned this limitation regarding the use of the clinical parameters not as a primary, but rather as a secondary outcome under the 'Strengths and limitations of this study'.

We have carefully considered the most relevant, feasible, and least burdensome measurement. We chose the intra-operative degree of collapse as a primary outcome, since we believe this is the most objective measure and has the lowest risk of bias. The objectivity of this measure is increased by the blinded assessment of TM, and by using the mean percentage of TM of all performed assessments. Furthermore, the risk of dropout is very low for this intra-operative TBS, since it takes place during the surgery.

All considerations above have been carefully weighed and have been approved by the Medical Ethics committees of the Netherlands and UK.

3. I profoundly disagree with your inclusion criteria of only randomizing those with collapse. The problem is your definition. What % will you consider severe enough to consider TBM. We well know that most of the time its not that obvious when they are newborns. Its also not customary for most surgeons to do a proper 3 phase dynamic bronchoscopy in a child with an active fistula as most surgeons and anesthesiologist are more worried about the active fistula and hence won't spend the appropriate time to perform an accurate diagnosis. Also, many times a child may be deemed as not having TBM preoperatively, and only to develop severe TBM shortly after repair. It is not reliable to base your diagnosis on preoperative bronchoscopy. I strongly believe you should include all newborns with type C, EA/TEF regardless of their initial bronchoscopy. This way you will have much less variability/surgeon bias/selection bias on the inclusion of patients. You can later stratify based on certain % collapse but I bet you that unless you have a central monitoring review of each preoperative bronchoscopy video (which you may want to consider anyway) you will not have a way to reliably diagnosis TBM pre-repair.

Response: We agree with the reviewer that it will be difficult to assess the percentage that would be needed to consider TBM during preoperative TBS and we would have preferred to include all OA/TOF patients. However, we suspected that the ethical committees of some European countries would not have approved if there were no signs of any tracheal collapse.

All participating centres have co-written an extensive standard operating procedure, stating that all patients will undergo a proper three-phase dynamic bronchoscopy (if the clinical state permits). To ensure the least selection-bias, all OA/TOF patients with any primary TM will be included. Only patients without any tracheal collapse or only secondary TM will be excluded. For this reason, the inclusion criteria in the protocol state only the presence of TM and not the absolute percentage. Moreover, the absolute percentage for TBM differs in literature, especially in children with OA, since there is no clear basis for a classification (3-5). Furthermore, the impact on the outcome is mitigated by stratifying by centre, through blinding of the video footage before assessment, and by using the mean of the measurements.

We also agree that many children develop severe TBM shortly after repair. The parameters for these patients will be evaluated in the sub-group that did not undergo a PPT. It will be interesting to discover which patients in the no-PPT group will develop TBM and which patients will not, since all will undergo intra- and postoperative TBS. Hopefully, this will help us understand the pathophysiology and henceforth guide us in determining which patients may benefit from PPT, even though their preoperative TBS did not show any signs of malacia.

4. For exclusion criteria why base it on gestational age? Why not weight instead? I'd say there are many kids who are 32-33 weekers with good weight who are good candidates. Maybe just limit it to <2kg or whatever you don't feel comfortable with. Also there is a flexible bronchoscope that is 2.2mm diameter so it can fit via a 2.5ETT, so not sure about your size 3 ETT exclusion criteria.

Response: We agree with the reviewer that weight could also have been an exclusion criterion and that some 32 week old neonates could be good candidates. The reason we chose gestational age is to decrease the impact of prematurity of less than 34 weeks old (6), to ensure all centres are able to treat the included patients and to therefore compare a homogeneous population.

A size 2.2 flexible bronchoscope will pass a size 2,5 endotracheal tube with difficulty and block the tube, thereby creating an airway obstruction which will influence the endoscopy greatly. Moreover, the size 2.2mm bronchoscope has a considerably lower resolution of video footage than the 2.7mm bronchoscope. This could make it possible to discern the video footage of smaller children from bigger children, thereby influencing blinding.

5. The other reason to avoid fixating on % collapse pre- to post-op is that we know that % collapse does not always correlate with symptomatology. Most of the time it does but not always. We have children who have great looking airways with no significant collapse and can have respiratory symptoms. While others can have significant collapse but no major symptoms. Key is to measure both but not get too fixated on % collapse. Symptoms are more important! One more reason to not fixate on % collapse is that you are forcing or exposing children to a second anesthetic just to measure their % collapse. What if they are not having symptoms? Would you still expose them to an anesthetic? I would not. Focus on symptoms!

Response: We agree with the reviewer that the clinical symptoms are most important. We kindly refer to our response on comment 2 and 3 for our reasoning behind using the intra-operative TBS as a primary outcome. This outcome measure ensures that data of as many patients as possible will be gathered (with low drop-out) and that it is comparable between centres.

Concerning the second comment on the anaesthetic exposure, patients who do not experience symptoms, will nevertheless be exposed to anaesthetic. For the patients at Great Ormond Street Hospital and at Karolinska University Hospital, this is standard of care if patients are diagnosed with TM during their preoperative TBS. This trial will therefore not expose these children to any additional burden. At Erasmus Medical Center and the University Medical Centre Utrecht, this investigation will be performed concurrently with a TBS on clinical indication or possibly with a clinically indicated esophagoscopy, minimising burden. In our experience, approximately 40-50% of patients undergo a clinically indicated TBS, and an additional 30% undergo at least one esophagoscopy, meaning approximately 20-30% of trial participants in the Netherlands will be exposed to anaesthetic for study purposes only. Furthermore, as the reviewer stated, the percentage of collapse usually, but not always, correlates with symptomatology. One of the secondary goals of this study is to evaluate whether the intraoperative or immediate postoperative TBS in the ICU can correlate with the postoperative TBS conducted 2-6 months later (during the second anaesthetic procedure). If our trial demonstrates this correlation, we hope to identify parameters associated with TM during the immediate postoperative TBS, potentially eliminating the need for a second postoperative TBS in the future.

Also, respiratory morbidity in OA patients is high. Many babies do not experience symptoms (yet), however, all OA patients participate in clinical longitudinal follow-up programs allowing us to follow the children. We hope to be able to obtain additional research funding, to eventually correlate the TBS findings with follow-up data on respiratory morbidity.

6. One of the technical things we have learned with doing several primary PTs is to place the pexy sutures (which by the way we recommend them being pledgeted with autologous tissue – pleura or azygous vein, and horizontal mattress) on the airway and spine but not tie them down until you have completed your esophageal dissection and ideally anastomosis (if you are doing it via thoracotomy), this way it makes the esophageal anastomosis easier and you are not tugging or pulling on a airway that is pexied to the spine as it can tear in a small delicate airway of a newborn. Yes, for a thoracoscopic anastomosis, it would be in the way so in that case yes the airway pexy goes before the anastomosis but only after you have completed your proximal esophageal pouch dissection.

Response: We agree with the reviewer that dissection of the proximal pouch is always performed before the tracheopexy is performed. These detailed steps are included in our standard operating procedure, which goes beyond the research protocol.

7. How will you ensure competency/equivalent surgical technique of these surgeons doing these primary tracheopexies in all these centers? How many have each of them done? Any training intervention? Monitoring of technique via video? Teleproctoring/mentoring?

Response: All participating centres are expert centres in the treatment of OA and have a vast experience in performing a posterior tracheopexy. To ensure all centres perform the

PPT as uniformly as possible, the first procedures in each centre will be performed together with an experienced surgeon from one of the other participating centres, either in person or through videoconference.

8. Please specify if your bronchoscopies will be rigid (with or without ventilating scope) or flexible. Ideally, need to keep them consistent. You may also want to standardize how the TEF is repaired (clips vs excision/fistulectomy vs simple ligation) – all of these can affect the risk of postop TBM..

Response: The type of bronchoscopy is indeed important to consider. The use of the flexible or rigid bronchoscopes is discussed in the protocol for the ethical committee, however not in this protocol paper as we believe the protocol for publication should be less detailed. All patients will undergo both flexible and rigid tracheobronchoscopy. As suggested by the reviewer, this has been altered to explicitly state so in section patient timeline (page 9, line 195). To illustrate which types of bronchoscopies are performed at which times, we have included Figure 1 below.

The method of TOF repair is not altered for study purposes, since standard of care for TOF repair is similar in all participating centres (i.e. dissection). However, the surgical approach (thoracoscopic or open) can vary between centres.

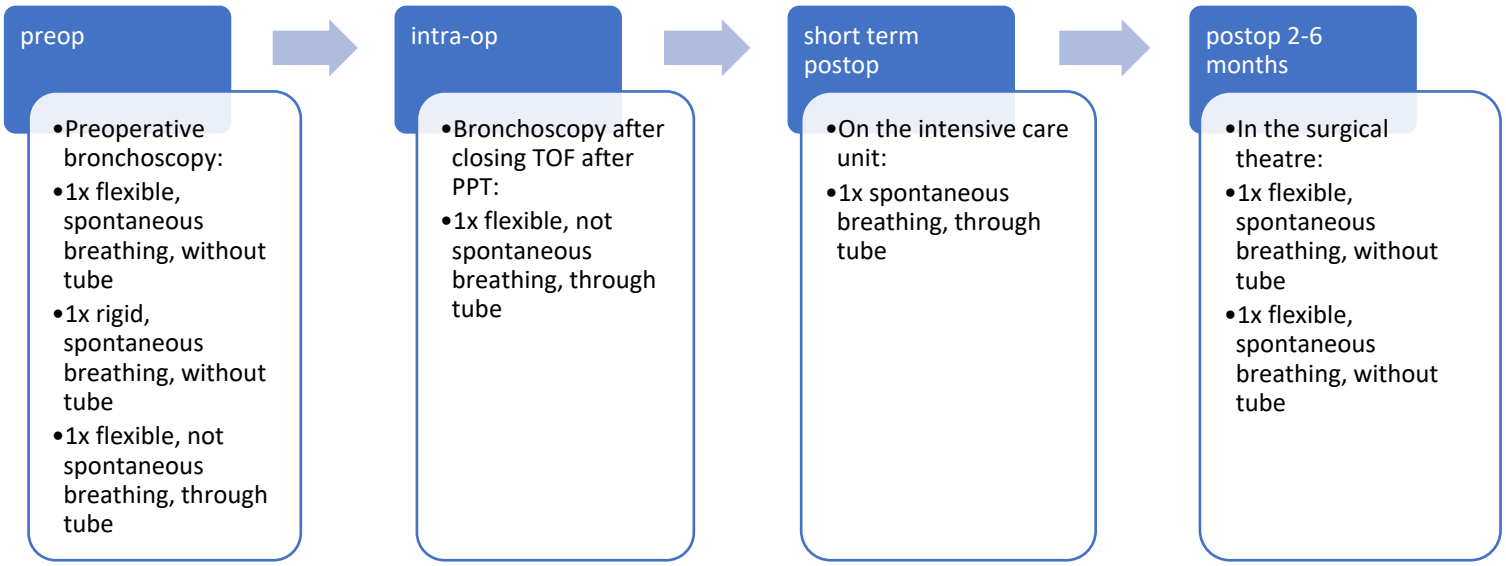

Figure 1. Bronchoscopies performed during trial

9. For complications I would strongly encourage you to assess vocal fold movement impairment. This is a highly underappreciated form of respiratory morbidity for these children and at such high risk for injury during EA repair (some data say that up to 1 in 4 children can present with VFMI after EA repair). This mean all children would need a preoperative assessment of vocal fold motion (as some can be born with congenital VFMI), and postoperative assessments as well. All being non-sedated with flexible nasolaryngoscopy or with ultrasound if you have experience with laryngeal ultrasound as it has been shown to be reliable/accurate as well.

Response: We agree with the reviewer that vocal fold movement needs to be assessed as well. This is already described in the standard operating procedure and will be recorded in the case report form for all tracheobronchoscopies without an endotracheal

tube.

10. A few other things. Would suggest you monitor symptoms not just for first 6 months but for first year to capture the true burden in the first year of life as it has been captured in other studies in order to compare things better. Also, would suggest you evaluate feeding scores in these children (such as mFOIS), as some of these kids with really bad airways from TBM struggle to eat. Also as secondary endpoints don't forget about how many got tracheostomies for severe TBM or other entities.

Response: We agree with the reviewer that a follow-up of 12 months would have been preferable. However, funding was obtained to facilitate a 6 month follow-up. We intend to obtain funding to facilitate a longer follow-up and further analyses. As previously mentioned, all OA patients participate in clinical longitudinal follow-up programs within our expert centres. Therefore, together with the intension of obtaining further funding, we hope to be able to include the clinical data gathered within the follow-up programs. In the patient informed consent form, we will ask for permission to use gathered data for future research and to contact patients for future research.

Feeding difficulties and behaviour will be documented in the case report form, as well as the number of tracheostomies and other surgical interventions.

References

1. Svetanoff WJ, Zendejas B, Frain L, Visner G, Smithers CJ, Baird CW, et al. When to consider a posterolateral descending aortopexy in addition to a posterior tracheopexy for the surgical treatment of symptomatic tracheobronchomalacia. J Pediatr Surg. 2020;55(12):2682-9.
2. Usui N, Kamata S, Ishikawa S, Sawai T, Okuyama H, Imura K, Okada A. Anomalies of the tracheobronchial tree in patients with esophageal atresia. J Pediatr Surg. 1996;31(2):258-62.
3. Bairdain S, Zurakowski D, Baird CW, Jennings RW. Surgical Treatment of Tracheobronchomalacia: A novel approach. Paediatr Respir Rev. 2016;19:16-20.
4. Tytgat S, van Herwaarden-Lindeboom MYA, van Tuyll van Serooskerken ES, van der Zee DC. Thoracoscopic posterior tracheopexy during primary esophageal atresia repair: a new approach to prevent tracheomalacia complications. J Pediatr Surg. 2018;53(7):1420-3.
5. Wallis C, Alexopoulou E, Anton-Pacheco JL, Bhatt JM, Bush A, Chang AB, et al. ERS statement on tracheomalacia and bronchomalacia in children. Eur Respir J. 2019;54(3).
6. Gouyon JB, Vintejoux A, Sagot P, Burguet A, Quantin C, Ferdynus C, Burgundy Perinatal N. Neonatal outcome associated with singleton birth at 34-41 weeks of gestation. Int J Epidemiol. 2010;39(3):769-76.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Obeida, Alaa**
Affiliation surgery	**Yorkshire and the Humber Postgraduate Deanery, General**

Date	**08-Sep-2024**
COI	**No competing interests.**

Thank you for addressing the issues raised in the first review. I got no further issues to highlight.

Reviewer	**2**
Name	**Zendejas, Benjamin**
Affiliation	**Boston Children's Hospital Department of Surgery**
Date	**01-Sep-2024**
COI	**None**

I disagree with your statement that % collapse is the most objective measure and lowest risk of bias. Even within our group, there is variability in the description of % collapse for a given airway. You may argue that it is more objective than symptoms alone but again, what does it matter if the child is asymptomatic? Anyway, I understand your impetus to use the % collapse as a metric for this study, as it is the "easy" thing to do. Yet I wanted to make sure you understood it is not the clinical relevant outcome (symptoms are). If this is the case, I strongly encourage you to have a central monitoring committee to video review all bronchoscopies and have an external reviewer (I'm happy to help with this if needed). Otherwise I worry your study outcomes won't be believable. Particularly if your main difference is a change in % collapse from 70% to 50%..sure its an improvement but without a formal validation process to ensure reliability between raters (need rater training/calibration etc), it will be hard to believe that those differences are not just due to chance or rater variation. If you establish a central review of all bronchoscopy videos you can limit this bias. In this day (in 2024) anyone can record a video, even if its with a smartphone and send it in. I strongly encourage you to do this.

VERSION 2 - AUTHOR RESPONSE

Reviewer 2
Dr. Benjamin Zendejas, Boston Children's Hospital Department of Surgery

Comments to the Author:
I disagree with your statement that % collapse is the most objective measure and lowest risk of bias. Even within our group, there is variability in the description of % collapse for a given airway. You may argue that it is more objective than symptoms alone but again, what does it matter if the child is asymptomatic? Anyway, I understand your impetus to use the % collapse as a metric for this study, as it is the "easy" thing to do. Yet I wanted to make sure you understood it is not the clinical relevant outcome (symptoms are). If this is the case, I strongly encourage you to have a central monitoring committee to

video review all bronchoscopies and have an external reviewer (I'm happy to help with this if needed). Otherwise I worry your study outcomes won't be believable. Particularly if your main difference is a change in % collapse from 70% to 50%..sure its an improvement but without a formal validation process to ensure reliability between raters (need rater training/calibration etc), it will be hard to believe that those differences are not just due to chance or rater variation. If you establish a central review of all bronchoscopy videos you can limit this bias. In this day (in 2024) anyone can record a video, even if its with a smartphone and send it in. I strongly encourage you to do this.

Response:

We agree with the reviewer that the symptoms are indeed the clinically relevant outcome, and we will certainly evaluate and report them during the entire duration of the trial and thereafter.

We also agree that there will be variability between the raters. This will be addressed by having two different raters from two different centres perform the video-assessments, and having them assess the same video twice. This will allow us to assess intra- and interobserver variability. The intraclass correlation coefficient (ICC) will be used to determine the agreement of the assessments made by the different raters. In addition, an ICC for the intra-rater agreement will be estimated.

As a formal validation process to ensure reliability and decrease bias, all video-assessments will be performed at the end of the study, pseudonymized and presented in a random order.

We thank the reviewer for the offer to help as an external reviewer, however, the regulations regarding personal data safety prohibit us to involve individual researchers/physicians who are not part of the research team.

The reviewer further states that the objectivity of the degree of tracheomalacia (TM) is not relevant if the child is asymptomatic. We agree that the degree of TM is not clinically relevant for the individual EA patient if this patient has no symptoms. However, in this trial, we will evaluate (the degree of) TM in relation to symptom development. We hope to identify parameters of the bronchoscopy that are associated with respiratory symptoms, as well as determine which degrees or types of tracheomalacia require (surgical) treatment.