

Peer Review File

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Response to Reviewer A

In general, please refrain from the use of non-common abbreviations such as PE as these trouble reading.

Reply/Changes in the text: Thank you for the comment, we have replaced all instances of “PE” with “pectus excavatum”.

In addition, as a second general comment, only few research groups published substantially on this niche subject in Q1 journals during the last years, including Nuss, Kelly, de Loos, Jaroszewski, Hebra, Haecker, et cetera. Surprisingly, only few papers were discussed or cited by the authors.

Reply/Changes in the text: Thank you for the comment and mention of authors that contributed to the literature in recent years. We have made an effort to include additional works by these groups in the review, particularly when discussing MIRPE techniques and modifications.

Introduction

• Line 52-53: don't you consider cosmetic discomfort and associated burden of disease as an indication for corrective surgery/treatment?

Reply: Thank you – we agree that the decision to treat pectus excavatum is guided by the patient's perception of cosmetic discomfort as a primary factor, supported by objective measures such as severity index and markers of physiologic compromise.

Changes in the text: We have modified the line in question and added a statement to reflect the above (see Page 3 Line 65-67, Page 8, Lines 198-199).

Methods

• Older studies were included when necessary. How were these then identified? Given the restrictions imposed on the PubMed search.

Reply: Thank you for the question – the initial search was done by a librarian, supplemented with earlier references to support certain statements in the review. On review, we agree that some of the historical references did not contribute meaningfully to the review and these were ultimately eliminated

Changes in the text: We have reviewed the inclusion of some of the older studies and removed them if they do not provide a compelling addition to the review or were summarized more effectively by more contemporary sources. We removed references detailing the early results of MIRPE which are now well established, as well as the comparisons between open and minimally invasive techniques (see, for example, deleted sections on Page 8 Line 210, page 10 line 295, page 13 line 444)

• Was the search performed by a certified librarian or the authors themselves?

Reply: The initial search was performed by a librarian and additional references were selected by the authors to support certain statements in the review – see above.

Changes in the text: We have included a statement in the methods to reflect this (see Page 4, Lines 91-92)

- Line 87 requires reference.

Reply: Thank you for the comment – we have included support for this statement.

Changes in the text: We have included 2 references that support improved exercise tolerance following pectus excavatum surgical repair (Jaroszewski and O’Keefe) – (see Page 5, Lines 105-107)

Main body

- With regards to preoperative evaluation: what is the position of chest CT and two-view plain radiographs. The latter can be used to determine the Haller index with reduced exposure to potentially harmful ionizing radiation. See for example: Sarwar, Zahir U., and Robert DeFlorio. "Pectus excavatum: current imaging techniques and opportunities for dose reduction." *Seminars in Ultrasound, CT and MRI*. Vol. 35. No. 4. WB Saunders, 2014.

Reply: Thank you for the comment – we agree it is important to highlight the use of CT and plain chest radiographs in the preoperative evaluation.

Changes in the text: We moved the discussion of preoperative imaging, including CT and X-ray from the ‘Monitoring’ section to the ‘Preoperative evaluation’ section and included the above reference as advised in order to round out the discussion on initial eval and imaging options (see Pages 6-7, Lines 149-172).

- In continuance on the previous comment: what is the position of simple photography of the chest?

Reply: Thank you for the comment – we agree it is relevant to include a statement on conventional photography and its limitations since it is so commonly used in clinical practice.

Changes in the text: We have added content and two reference on conventional photography that describe both its use in clinical practice and limitations, as advised (see Page 7, Lines 172-179).

- Moreover, previous reports show that 3D scanning/imaging of the chest can be used to determine surgical candidacy through a derivative of the conventional Haller index. It is moreover able to even predict the presence of cardiac compression! See: (Daemen JHT, Coorens NA, Hulsewé KWE, Maal TJJ, Maessen JG, Vissers YLJ, de Loos ER. Three-dimensional surface imaging for clinical decision making in pectus excavatum. *Semin Thorac Cardiovasc Surg* 2021.) AND (Daemen JHT, Heuts S, Rezazadah Ardabili A, Maessen JG, Hulsewé KWE, Vissers YL, de Loos ER. Development of prediction models for cardiac compression in pectus excavatum based on three-dimensional surface images. *Semin Thorac Cardiovasc Surg* 2021.)

Reply: Thank you for bringing this to our attention – the more recent reports of the applications of 3D-imaging beyond simple correlation with existing indices are relevant and worth including in the discussion.

Changes in the text: We have added content reflecting the above comments relating to 3D imaging and predicting surgical candidacy and cardiac compression (see Pages 7-8, Lines 187-193).

- Despite the improved pulmonary parameters often seen (only after Nuss bar removal), this is not considered clinically relevant. The main improvement in cardiopulmonary exercise tolerance is due to the resolved cardiac compression. This is best demonstrated by the fact that pulmonary parameters often deteriorate after Nuss bar implantation due to increased chest rigidity (without pulmonary symptoms) and only improve after Nuss bar removal. See for example also: Malek, Moh H., Eric W. Fonkalsrud, and Christopher B. Cooper. "Ventilatory and cardiovascular responses to exercise in patients with pectus excavatum." *Chest* 124.3 (2003): 870-882.

Reply: Thank you for the insight into the primary physiologic effect contributing to exercise tolerance in this population – we agree that this deserves specific mention and greater emphasis than the changes in pulmonary parameters that we had included.

Changes in the text: We modified the text to include content on pectus-related cardiac compression from Malek, et al and also referenced Jaroszewski et al to support the statement about pulmonary parameters declining after initial Nuss bar placement, then improving after removal (see Pages 5-6. Lines 118-141)

- It may be informative to state that especially pediatric patients less often suffer from chronic pain complaints after surgery. See: de Loos ER, Pennings AJ, van Roozendaal LM, Daemen JHT, van Gool MH, Lenderink T, van Horck M, Hulsewé KWE, Vissers YLJ. Nuss procedure for pectus excavatum: a comparison of complications between young and adult patients. *Ann Thorac Surg* 2020;112:905-11.

Reply: Thank you for the comment – we agree this would be a relevant piece of information to include when discussing postoperative pain, including the discussion of cryoablation, as adults have been found to experience more prolonged neuropathic pain symptoms compared to pediatric patients.

Changes in the text: We have added the above statement as suggested when discussing postoperative pain in this population and also in the discussion of response to cryoablation (See Page 15 Lines 537-540 and Pages 16-17 Lines 578-587)

- Any thoughts on the use of different bar configurations? Which is the best? Cross-bar, parallel, single, sandwich etc In addition, anything about the bar curvature etc? see for example: Pérez, D., Martel, O., Yáñez, A., Cano, J. R., Cuadrado, A., Torrent, G., & López, L. (2020). Does the modelling of the pectus bar affect its stability? *Rationale for using a short flat bar. Interactive CardioVascular and Thoracic Surgery*, 30(1), 11-17.

Reply: Thank you.– As you point out, a great deal of work has recently been done evaluating different bar configurations, and we agree this should be a key focus of the MIRPE discussion, especially given the many variations in recent literature (particularly by Pilegaard, Park, Hebra, etc)

Changes in the text: We have added content describing the technical aspects of MIRPE including the merits of various bar configuration and stabilization mechanisms. We have mentioned multiple bars, cross-bar, lateral and medial stabilizers, bridge technique, and bar shape – including short/flat bars (with the suggested reference) and bending techniques (See Pages 10-12, Lines 309-406).

- One of the major disadvantages of the current non-surgical treatment options is patient compliance being the primary reason for treatment failure. In addition, there is no data on long-term effect.

Reply: We agree with this assessment and have had a similar experience in following our own vacuum bell population.

Changes in the text: We have added a statement to reflect the above position when discussing vacuum bell therapy (see Page 15, Lines 527-532)

- Given that studies were selected based on the level of evidence it would be good to add a recent systematic review and meta-analysis on intercostal nerve cryoablation which outperforms the level of evidence currently provided. (see: Daemen JHT, de Loos ER, Vissers YLJ, Bakens M, Maessen JG, Hulsewé KWE. Intercostal nerve cryoablation versus thoracic epidural for postoperative analgesia following pectus excavatum repair: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2020;31:486-98)

Reply: Thank you for the suggestion – we agree that including a systematic review and meta-analysis would bolster the argument with a higher level of evidence.

Changes in the text: We have included the above referenced systematic review in our discussion of intercostal nerve cryoablation vs epidural analgesia (see Page 16, Lines 570-572)

- Can you tell anything about the learning curve of the surgical procedures?

Reply: Thank you for the comment – we agree that a discussion on the learning curve for MIRPE is worth including in the text.

Changes in the text: We have added a paragraph at the end of the MIRPE section that two references that discuss learning curve with regard to MIRPE (see Page 13, Lines 418-425).

- The best intended method for monitoring would be 3D imaging/scanning with automated measurements of the deformity! See the available literature on this subject. Its not a future thing but readily available.

Reply: We agree that 3D chest imaging would be the ideal method for monitoring while avoiding ionizing radiation and our group has started incorporating this technology into our own workflow.

Changes in the text: We have added a statement reflecting the above in the “Monitoring” section and also discuss 3D imaging initially in the “Preoperative evaluation” section (see Page 18, Lines 627-632).

- Regarding the paragraph on 3D imaging and its correlation to indices! We are already way further, see above mentioned citations!

Reply: Thank you for the comment – we agree there are broader reaching applications of 3D surface imaging which deserve to be mentioned

Changes in the text: Similar to above response - we have incorporated additional literature/commentary on 3D imaging aside from correlation to indices – both in the Introduction and monitoring sections (see Pages 7-8, Lines 181-193).

- As a last comment, It would be good to stress the lack of (international) guidelines on the preoperative evaluation and treatment of pectus excavatum, especially to guide future research.

Reply: This is a very interesting point – and the lack of such an international guideline may contribute to very divergent practices worldwide.

Changes in the text: We have modified our text as advised and included the above statement in the conclusion (see Page 19, Lines 655-658).

Response to Reviewer B

Authors have written a comprehensive up to date review on pectus excavatum repair. Only error that I see is on Line 320:

Keller and colleagues were the first to describe the use of INC in MIRPE in 2016; they demonstrated a significant reduction in opioid use and LOS when compared to epidural analgesia, with a mean LOS of 3.5 days in the cryo group (49). Ref: J Pediatr Surg. 2016 Dec;51(12):2033-2038. doi: 10.1016/j.jpedsurg.2016.09.034. Epub 2016 Sep 28. PMID: 27745867. Keller paper was published in December 2016, in which they neglected to mention the earlier report. He describes cryoablation of the intercostal nerve using a SUBCUTANEOUS approach.

Correct first report of cryoanalgesia was published in the Journal of Thoracic Cardiovascular Surgery March 2016, 9 month earlier than Keller et al: Use of transthoracic cryoanalgesia during the Nuss procedure. Kim S, Idowu O, Palmer B, Lee SH. J Thorac Cardiovasc Surg. 2016 Mar;151(3):887-888. doi: 10.1016/j.jtcvs.2015.09.110. PMID: 26896363. This paper describes INTRATHORACIC cryoablation method which is the current method used by most surgeons. This error should be corrected.

Reply: Thank you for the comment and correction of the first description of intrathoracic cryoablation.

Changes in the text: We have modified our text as advised and replaced with the appropriate reference (see Page 16, Lines 563-567)

Response to Reviewer C

The authors present a comprehensive narrative review on the management of Pectus excavatum in Pediatric patients. The focus of the manuscript is not within the scope of a scientific journal, but maybe of a textbook. The current version of the manuscript might be considered as a chapter for a textbook.

Of course, there are numerous publications dealing with this topic, and it is nearby impossible to review all the literature. Even if some of the most important articles are mentioned in the list of references, I cannot follow the statement that the articles were examined for relevancy.

What is the intension to compare results of open surgical repair vs. minimally invasive repair published more than 20 years ago? All pectus surgeons know about their personal learning curve, and their results are much better after 20 years experience.

Even if the autohrs include a remarkable number of publications, I consider the manuscript in the current version as not appropriate for publication in a scientific journal. Please find my comments above.

Reply: Thank you for the comments and assessment of the manuscript. We see how the inclusion of a number of historical references and comparisons contributed to the “textbook-like” tone of the manuscript. We also agree that MIRPE is the dominant practice and gold standard in contemporary pectus treatment. Recent techniques and variations should therefore be the emphasis of a contemporary surgical review on the topic, in addition to novel imaging and monitoring strategies. We have therefore re-focused the manuscript to trim the superfluous

historical content, while emphasizing the current approaches and controversies in management and feel this is better suited for publication in a scientific journal.

Changes in the text: Within the introduction and preoperative evaluation, we included content on the relevant imaging modalities and physiologic impact using more contemporary sources (see Pages 6-8, Lines 149-195). Within the surgical discussion, we focused on MIRPE and described the technical aspects of various bar configurations including multiple bars, cross-bar, lateral and medial stabilizers, bridge technique, and bar shape (See Pages 10-12, Lines 309-406). We removed references detailing the early results and complications of MIRPE which are now well-established (and likely less relevant when taking into account the appropriate learning curve) and de-emphasized the open vs minimally invasive discussion (see, for example, deleted sections on Page 8 Line 210, page 10 line 295, page 13 line 444). We also reinforced the monitoring section with additional information on 3D imaging and future directions (see Pages 18-19, Lines 627-651).