Peer Review File

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Reviewer A

Comment 1: The title is too unspecific. That would be suitable for a book chapter, but for a journal article it needs to be more concrete
Response 1: This manuscript is for a special edition of reviews and we have used the title approved by the journal. We have not changed this currently, but would be happy to do so if the editor felt it important.

Comment 2: Do you have experience with the endoballoon technique? What are advantages and pitfalls compared to conventional clamping?
Response 2: Thank you for raising this. We have expanded the section "Aortic cross clamping" with discussion about a recently published meta-analysis which compared endoaortic clamping vs external clamping.

Added text: "The endoclamp offers functions in addition to clamping which are not offered by the external clamp. These include the ability to deliver cardioplegia, vent the aortic root, and monitor aortic root pressure through the tip of the endoballoon (Khan et al., 2018). Disadvantages include movement of the endoballoon within the aortic lumen which may not be visible during the procedure, necessitating the use of bilateral axillary pressure monitoring to detect displacement (Van Praet et al., 2018). An alternative to both the aortic endoclamp and the external Chitwood clamp is the external Cygnet device (Novare Surgical Systems, USA) which does not require an additional port and can be used through the main operating port (Khan et al., 2018). In terms of outcomes, a meta-analysis from 2018 demonstrated that use of aortic endoclamping during minimally invasive surgery carried higher pooled risk of both aortic dissection (OR = 3.88, 95% CI = 1.06–14.18; P =0.04) and conversion to sternotomy (OR = 3.07, 95% confidence interval = 1.33–7.10; P = 0.009). However, the authors of that study clarify that when each study was analysed individually there was no increase in risk for both outcomes between endoclamping and external clamping patient groups. Thus, considering that the primary literature consists of non-randomised cohorts, the authors suggest that with enough experience in using both techniques, other centres will be able to produce similar results between each technique (Khan et al., 2018)."

New reference:
Khan, H., Hadjittofi, C., Uzzaman, M., Salhiyyah, K., Garg, S., Butt, S., Aya, H., Chaubey, S., & Khan, H. (2018). External aortic clamping versus endoaortic balloon occlusion in minimally inva-sive cardiac surgery: a systematic review and meta-analysis External aortic clamping versus endoaortic balloon occlusion in minimally invasive cardiac surgery: a systematic

review and meta-analysis. Interact CardioVasc Thorac Surg, 27(2), 208–222. https://doi.org/10.1093/icvts/ivy016

Comment 3: Comparing the right thoracotomy approach to standard sternotomy you mention the prolonged CPB and cross clamp times which I would see as a disadvantage – you do not explain at all, why someone should prefer the disadvantageous access.
Response 3: We have highlighted several advantages of the MIMVS approach throughout the manuscript and expanded on these benefits. Additionally, we have added new discussions concerning benefits in terms cost, postoperative complications and patient satisfaction (please see responses to Reviewers B and D). To make this point even more clear, we have also added some text to the conclusion.

Added text: "MIMVS is becoming increasingly widespread in cardiac surgical units globally. This is most commonly performed through a right anterolateral thoracotomy. Numerous studies have now shown favourable early and late clinical outcomes, in terms of in-hospital mortality, recurrence of mitral regurgitation or need for re-intervention. There is certainly a learning curve associated with this procedure (Holzhey et al., 2013) and there are challenges posed by the limited operative field including considerations relating to cardiopulmonary bypass and myocardial preservation. Despite some technical drawbacks such as prolonged CPB and cross clamp times, MIMVS remains equivalent to the standard sternotomy approach in terms of outcomes. Furthermore, MIMVS is associated with decreased postoperative hospital stays, reduced requirements of blood transfusion, cost savings and importantly, patient satisfaction. Therefore, although it is clear that patient selection is important, particularly early in a surgical programme, with experience complex repairs can be performed through a minimally invasive approach with excellent outcomes."

Comment 4: A professional English editing service is recommended.
Response 4: We have reviewed the text and made changes as appropriate

Reviewer B
Comment 1: The authors should address the total number of mitral valve surgery performed globally and how many of them are performed MMVS versus standard sternotomy
Response 1: Thank you for this comment. We agree that this would be interesting information. However, despite searching the literature and even our national societies publications it is not possible for us to find reliable data on the number of cases being performed and so we have not been able to address this point.

Comment 2: The authors need to add a paragraph on the history of MMVS paying tribute to the major think tanks in the field who popularized and developed the technique.
Response 2: We have expanded the introduction by acknowledging the historical evolution of this field and the pioneering groups who popularised this technique.

The following text was added to the introduction: “The history of MIMVS extends from the 1990s when minimally invasive approaches such as the parasternal incision, hemisternal incision and the mini-thoracotomy were first explored by independent groups led by Delos Cosgrove and Lawrence Cohn (Cohn et al., 1997; Modi et al., 2008; Navia & Cosgrove, 1996). Subsequent developments include the first video-directed repair (Carpentier et al., 1996) and replacements (J. Chitwood et al., 1997; W. R. Chitwood et al., 1997) performed through a mini-thoracotomy, and the first use of aortic endoballoon clamping. More recent developments include the advent of stereoscopic three-dimensional video-endoscopy and robotic surgery.”

New references added:

- Carpentier, A., Loulmet, D., Carpentier, A., Le Bret, E., Haugades, B., Dassier, P., & Guibourt, P. (1996). [Open heart operation under videosurgery and minithoracotomy. First case (mitral valvuloplasty) operated with success]. Comptes Rendus de l’Academie Des Sciences. Serie III, Sciences de La Vie, 319(3), 219–223.
- Chitwood, J., Elbeery, J. R., Chapman, W. H. H., Moran, J. M., Lust, R. L., Wooden, W. A., & Deaton, D. H. (1997). Video-assisted minimally invasive mitral valve surgery: The “micro- mitral” operation. Journal of Thoracic and Cardiovascular Surgery, 113(2), 413–414. https://doi.org/10.1016/S0022-5223(97)70341-6
- Chitwood, W. R., Elbeery, J. R., & Moran, J. F. (1997). Minimally invasive mitral valve repair using transthoracic aortic occlusion. Annals of Thoracic Surgery, 63(5), 1477–1479. https://doi.org/10.1016/S0003-4975(97)00242-7
- Cohn, L. H., Adams, D. H., Couper, G. S., Bichell, D. P., Rosborough, D. M., Sears, S. P., & Aranki, S. F. (1997). Minimally invasive cardiac valve surgery improves patient satisfaction while reducing costs of cardiac valve replacement and repair. Annals of Surgery, 226(4), 421–428. https://doi.org/10.1097/00000658-199710000-00003

Comment 3: The authors refer to non-rib spreading type MMVS without mentioning the role of 3-Dimensional endoscopic mitral valve developed in Belgium. This should be mentioned.

Response 3: Thank you for the suggestion. We have added some text under the “Mini-thoracotomy surgical technique” section to acknowledge this. However, 3-D endoscopic technology plays a larger role in robotic mitral valve surgery, which is out of the scope of this article and is discussed in another article in this series.

Added text: “Additionally, stereoscopic endoscopy allowing for three-dimensional vision is an emerging technology which gives surgeons superior depth perception during surgery (W. R. Chitwood & Nifong, 2000; Kypson et al., 2003; H. Reichenspurner et al., 1999; Hermann Reichenspurner et al., 2000). This is being increasingly adopted across many centres

worldwide although it sees much more use in robotic surgery. Robotic MIMVS is beyond the scope of the current article and is discussed in another chapter of this article series."

New references added:

- Chitwood, W. R., & Nifong, L. W. (2000). Minimally Invasive Videloscopic Mitral Valve Surgery: The Current Role of Surgical Robotics. Journal of Cardiac Surgery, 15(1), 61–75. https://doi.org/10.1111/j.1540-8191.2000.tb00445.x
- Kypson, A. P., Nifong, W. W., & Chitwood, W. R. (2003). Robotic mitral valve surgery. Seminars in Thoracic and Cardiovascular Surgery, 15(2), 121–129. https://doi.org/10.1016/S1043-0679(03)70020-3
- Reichenspurner, H., Boehm, D., & Reichart, B. (1999). Minimally invasive mitral valve surgery using three-dimensional video and robotic assistance. Seminars in Thoracic and Cardiovascular Surgery, 11(3), 235–243. https://doi.org/10.1016/S1043-0679(99)70064-X Reichenspurner, Hermann, Boehm, D. H., Gulbins, H., Schulze, C., Wildhirt, S., Welz, A., Detter, C., & Reichart, B. (2000). Three-dimensional video and robot-assisted port-access mitral valve operation

Comment 4: While the stat does not support any difference in outcomes other than cosmesis, the authors need to compare the costs of MMVS versus sternotomy particularly with reference for more time needed and special equipment required in the former compared to sternotomy

Response 4: This is indeed a valid question and we have addressed this in our discussion.

In the section "Comparison of the mini right thoracotomy approach vs sternotomy", we have added the text: "Finally, the cost of the procedure must be considered, especially in the context of MIMVS requiring longer operative times and more specialised operative instruments (Botta et al., 2013). Despite these factors, numerous studies suggest that MIMVS may be cheaper than conventional sternotomy operations (J. Chitwood et al., 1997; W. R. Chitwood & Nifong, 2000; Cohn et al., 1997; Cosgrove et al., 1998; Downs et al., 2016; Gersak et al., 2005; Grossi et al., 2014; Iribarne et al., 2011, 2012). Cost savings appear to be driven by a combination of shorter hospital stays, reduced incidence of complications such as sepsis and reduced requirement of postoperative blood transfusion (Santana et al., 2015)."

New references:

- Botta L, Cannata A, Bruschi G, et al. Minimally invasive approach for redo mitral valve surgery. J. Thorac. Dis. 2013;5(SUPPL.6).
- Grossi EA, Goldman S, Wolfe JA, et al. Minithoracotomy for mitral valve repair improves inpatient and postdischarge economic savings. J. Thorac. Cardiovasc. Surg. 2014;148(6):2818-2822.e3.

• Iribarne A, Easterwood R, Russo MJ, et al. A minimally invasive approach is more cost-effective than a traditional sternotomy approach for mitral valve surgery. J. Thorac. Cardiovasc. Surg. 2011;142(6):1507–1514.
• Iribarne A, Easterwood R, Russo MJ, et al. Comparative effectiveness of minimally invasive versus traditional sternotomy mitral valve surgery in elderly patients. J. Thorac. Cardiovasc. Surg. 2012;143(4 SUPPL.).
• Gersak B, Sostaric M, Kalisnik JM, et al. The preferable use of port access surgical technique for right and left atrial procedures. Heart Surg. Forum. 2005;8(5).
Cosgrove DM, Sabik JF, Navia JL. Minimally invasive valve operations. Ann. Thorac. Surg. 1998;65(6):1535–1539

Comment 5: The author provides a myriad of techniques in myocardial protection, bypass, and aortic clamping. The author can provide a table to demonstrate the benefits and negatives comparing and contrasting the techniques.
Response 5: Thank you. We have summarised various techniques which may be used for CPB, aortic cross clamping and myocardial protection in MIMVS and their benefits/use cases and disadvantages. These are presented in a new Table 3.

Changes made: a new Table 3 has been added.

Comment 6: Patients are now more informed, and cardiologists prefer to send these patients to reference centers of mitral valve repair. The authors should review the patient experience and attitudes toward undertaking small access approach surgery in general in the literature before and after MMVS versus sternotomy for example and reference this work in the review
Response 6: Patient satisfaction is indeed a key metric to be considered when evaluating surgical options and providing patients with informed choices. Thus, we have acknowledged this by adding text to the section “Comparison of the mini right thoracotomy approach vs sternotomy”.

Added text: “In addition to the improvements in cosmesis over conventional surgery, MIMVS patients also report increased satisfaction in terms of feeling ready to return to work, normal activity and improvements in subjective feeling (Cohn et al., 1997).”

Reference:
Cohn LH, Adams DH, Couper GS, et al. Minimally invasive cardiac valve surgery improves patient satisfaction while reducing costs of cardiac valve replacement and repair. Ann. Surg. 1997;226(4):421–428.

Reviewer C

Comment 1: The Authors wrote a review article on minimally invasive mitral valve surgery. This review is, more or less, a list of what has to be done to perform a MIMV procedure, either repair or replacement. Comparing MV surgery via a minimally access or via a median sternotomy is really complex. Most of the Authors have a precise case selections for MIMV surgery, and, honestly, any comparison is difficult. Good results can be obtained, but a bias in the selection avoids to state that MIMV surgery is similar to median sternotomy. This paper does not add anything to what we know. The real problem of MIMV surgery is the learning curve, the ability of a surgeon to perform good MV repair via a median sternotomy and his capability to transfer this knowledge in a small operative field, the number of cases necessary to obtain good results, and so on.
Response 1: Thank you for your comments. We agree generally with the reviewers assessment. We hope that with our changes made in response to the other reviewers comments we have gone some way to address some of the issues that this reviewer has raised.

Reviewer D
Comment 1: In order to increase the significance of the paper, the Authors should provide literature-based conclusions on more specific outcomes, including for example postoperative transfusion rates, duration of mechanical ventilation…
Response 1: We have discussed some of these outcomes when comparing MIMVS and conventional surgery in the section "Comparison of the mini right thoracotomy approach vs sternotomy". Alluding to the reduced post-operative transfusion rates we have found several studies which suggest that MIMVS confers a significant benefit in minimising blood produce usage. Also please refer to the comment by Reviewer B above relating to the cost benefits of MIMVS.

We have added the following text: "Finally, the cost of the procedure must be considered, especially in the context of MIMVS requiring longer operative times and more specialised operative instruments (Botta et al., 2013). Despite these factors, numerous studies suggest that MIMVS may be cheaper than conventional sternotomy operations (J. Chitwood et al., 1997; W. R. Chitwood & Nifong, 2000; Cohn et al., 1997; Cosgrove et al., 1998; Downs et al., 2016; Gersak et al., 2005; Grossi et al., 2014; Iribarne et al., 2011, 2012). Cost savings appear to be driven by a combination of shorter hospital stays, reduced incidence of complications such as sepsis and reduced requirement of postoperative blood transfusion (Santana et al., 2015)".

New references added:

- Botta L, Cannata A, Bruschi G, et al. Minimally invasive approach for redo mitral valve surgery. J. Thorac. Dis. 2013;5(SUPPL.6).

• Grossi EA, Goldman S, Wolfe JA, et al. Minithoracotomy for mitral valve repair improves inpatient and postdischarge economic savings. J. Thorac. Cardiovasc. Surg. 2014;148(6):2818-2822.e3.
• Iribarne A, Easterwood R, Russo MJ, et al. A minimally invasive approach is more cost-effective than a traditional sternotomy approach for mitral valve surgery. J. Thorac. Cardiovasc. Surg. 2011;142(6):1507–1514.
• Iribarne A, Easterwood R, Russo MJ, et al. Comparative effectiveness of minimally invasive versus traditional sternotomy mitral valve surgery in elderly patients. J. Thorac. Cardiovasc. Surg. 2012;143(4 SUPPL.).
• Gersak B, Sostaric M, Kalisnik JM, et al. The preferable use of port access surgical technique for right and left atrial procedures. Heart Surg. Forum. 2005;8(5).
Cosgrove DM, Sabik JF, Navia JL. Minimally invasive valve operations. Ann. Thorac. Surg. 1998;65(6):1535–1539.

Comment 2: The various technical options are not mentioned. In example, the paragraph about aortic cross-clamp cites the Chitwood transcutaneous clamp and the endoaortic balloon occluder are cited, but other devices exist (such as the Cygnet clamp avoiding the additional incision required for the Chitwood clamp) is not described
Response 2: Thank you. As Reviewer A has also suggested we now discuss aortic clamp techniques in greater detail, we have significantly expanded the discussion on types of aortic clamping. We have thus discussed both endoballoons as well as the Cygnet clamp. This has been added to the section “Aortic cross clamping”.

Added text: “The endoclamp offers functions in addition to clamping which are not offered by the external clamp. These include the ability to deliver cardioplegia, vent the aortic root, and monitor aortic root pressure through the tip of the endoballoon (Khan et al., 2018). Disadvantages include movement of the endoballoon within the aortic lumen which may not be visible during the procedure, necessitating the use of bilateral axillary pressure monitoring to detect displacement (Van Praet et al., 2018). An alternative to both the aortic endoclamp and the external Chitwood clamp is the external Cygnet device (Novare Surgical Systems, USA) which does not require an additional port and can be used through the main operating port (Khan et al., 2018). In terms of outcomes, a meta-analysis from 2018 (Khan et al., 2018) demonstrated that use of aortic endoclamping during minimally invasive surgery carried higher pooled risk of both aortic dissection (OR = 3.88, 95% CI = 1.06–14.18; P =0.04) and conversion to sternotomy (OR = 3.07, 95% confidence interval = 1.33–7.10; P = 0.009). However, the authors of that study clarify that when each study was analysed individually there was no increase in risk for both outcomes between endoclamping and external clamping patient groups. Thus, considering that the primary literature consists of non-randomised cohorts, the authors suggest that with enough experience in using both techniques, other centres will be able to produce similar results between each technique (Khan et al., 2018).”

New reference:
Khan, H., Hadjittofi, C., Uzzaman, M., Salhiyyah, K., Garg, S., Butt, S., Aya, H., Chaubey, S., & Khan, H. (2018). External aortic clamping versus endoaortic balloon occlusion in minimally invasive cardiac surgery: a systematic review and meta-analysis External aortic clamping versus endoaortic balloon occlusion in minimally invasive cardiac surgery: a systematic review and meta-analysis. Interact CardioVasc Thorac Surg, 27(2), 208–222

Comment 3: The current availability of 3D cameras is expected to greatly enhance the reproducibility of MIMVS, but this is not cited in the manuscript and its potential role is not addressed
Response 3: Thank you. We have now discussed the use of 3D cameras in our text as well as acknowledged the role of stereoscopic vision in recent developments in MIMVS – please see response to Reviewer B above.

The following text has been added to section "Mini-thoracotomy surgical technique":
"Additionally, stereoscopic endoscopy allowing for three-dimensional vision is an emerging technology which gives surgeons superior depth perception during surgery (W. R. Chitwood & Nifong, 2000; Kypson et al., 2003; H. Reichenspurner et al., 1999; Hermann Reichenspurner et al., 2000). This is being increasingly adopted across many centres worldwide although it sees much more use in robotic surgery. Robotic MIMVS is beyond the scope of the current article and is discussed in another chapter of this article series."

New references added:
- Chitwood, W. R., & Nifong, L. W. (2000). Minimally Invasive Videloscopic Mitral Valve Surgery: The Current Role of Surgical Robotics. Journal of Cardiac Surgery, 15(1), 61–75. https://doi.org/10.1111/j.1540-8191.2000.tb00445.x
- Kypson, A. P., Nifong, W. W., & Chitwood, W. R. (2003). Robotic mitral valve surgery. Seminars in Thoracic and Cardiovascular Surgery, 15(2), 121–129. https://doi.org/10.1016/S1043-0679(03)70020-3
- Reichenspurner, H., Boehm, D., & Reichart, B. (1999). Minimally invasive mitral valve surgery using three-dimensional video and robotic assistance. Seminars in Thoracic and Cardiovascular Surgery, 11(3), 235–243. https://doi.org/10.1016/S1043-0679(99)70064-X Reichenspurner, Hermann, Boehm, D. H., Gulbins, H., Schulze, C., Wildhirt, S., Welz, A., Detter, C., & Reichart, B. (2000). Three-dimensional video and robot-assisted port-access mitral valve operation. Annals of Thoracic Surgery, 69(4), 1176–1181. https://doi.org/10.1016/S0003-4975(99)01561-1

Comment 4: Evidence exist about specific advantages of MIMVS in particular patients' subsets, the current manuscript being limited to the 'generic' patients' population only. In example, redo patients were the MIMVS approach has been associated with significant

reduction of some morbidities. Other patients' subsets (i.e., the elderly, the obese…) have been the object of dedicated investigations. Addressing such data would in my opinion enhance the value of the manuscript and its messages.
Response 4: We have acknowledged the attractiveness of MIMVS in challenging subgroups of patients including patients undergoing redo procedures and patients considered "high risk".

We have added the following text to the section "Patient selection": "MIMVS may have a role in redo mitral valve surgery, with studies reporting ranges of 1-35.6% of MIMVS being redo procedures (Botta et al., 2013). This is especially useful when reopening of the sternum is to be avoided, which avoids the risk of damaging cardiac structures, adhesions from prior surgeries and coronary grafts (Botta et al., 2013). Another attractive niche of patients is those who would be considered "high risk" for conventional surgery. There appears to be acceptable outcomes in these cases (in terms of postoperative recovery and mortality) which includes populations of patients with infective endocarditis, previous cardiac surgery and age > 75 (Moscarelli et al., 2016)."

New references:

- Botta L, Cannata A, Bruschi G, et al. Minimally invasive approach for redo mitral valve surgery. J. Thorac. Dis. 2013;5(SUPPL.6).

Moscarelli M, Casula R, Speziale G, et al. Can we use minimally invasive mitral valve surgery as a safe alternative to sternotomy in high-risk patients? Interact. Cardiovasc. Thorac. Surg. 2016;22(1):92–96