Author's response to reviews

Title: Early Impact of Aortic Wrapping on Patients Undergoing Aortic Valve Replacement with Mild to Moderate Ascending Aorta Dilatation

Authors:

Keng-Leong Ang (ka106@le.ac.uk)
Furqan Raheel (furgan.raheel@uhl-tr.nhs.uk)
Amrita Bajaj (amrita.bajaj@uhl-tr.nhs.uk)
Andrzej Sosnowski (sue.holleworth@uhl-tr.nhs.uk)
Manuel Galinanes (mg50@le.ac.uk)

Version: 2 Date: 11 June 2010

Author's response to reviews:

Reviewer's report
Title: Aortic wrapping for mild to moderate ascending aorta dilatation is associated with early favourable aortic remodelling

Version: 1 Date: 23 March 2010
Reviewer: Vipin Zamvar

Reviewer's report:
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
None
Response: We are very grateful for the positive comments. Thanks.

AORTIC WRAPPING FOR MILD TO MODERATE ASCENDING AORTA DILATATION IS ASSOCIATED WITH EARLY FAVOURABLE AORTIC REMODELLING
Authors: Keng-Leong Ang*1,, Furqan Raheel*1, Amrita Bajaj2, Andrzej Sosnowski1,
Manuel Galinanes1
Review – Professor Anthony Mathur  
Department of Cardiology  
London Chest hospital  
Bonner Road,  
London E2 9JX  

1. Is the question posed by the authors new and well defined?  
The authors explain the background questions surrounding this problem which seems to be new and pertinent for those working in the field.  
Response: Thank you for the comments on the importance of our study.  

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?  
The paper is descriptive with a small number of patients. There is no control group and so no idea of the natural history of the condition in this group of patients particularly since they have the confounder of aortic valve surgery in addition to the Dacron graft.  
Response: There is very limited information on the natural history of the condition in this group of patients, especially in the context of concomitant aortic valve surgery. This is a preliminary study and not a randomized study and therefore there is no control group. This point has been clarified in the revised manuscript. In addition, we have expanded on this point in the background (page 3) and the discussion (page 8).  

3. Are the data sound and well controlled?  
The limited data appears sound although no indication is given regarding the reproducibility of the aortic dimensions. This should be included. There is no control and no mention of other historical data regarding changes in aortic dimensions following aortic valve replacement. This should be added.  
Response: Thank you again for these points. Measurements were made by a single, but experienced observer, a point clarified on page 9. Furthermore, as mentioned, above, we have incorporated the additional suggestions in the background (page 3) and the discussion (page 8).  

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
As far as it goes – yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
The discussion should re-iterate that this is a very small study with no control group and no long-term follow up. There is nothing in this paper to suggest that this procedure will benefit these patients and this point should be re-emphasized. Concluding that the procedure is safe should be qualified by short-term. Long-term erosion of the graft is not known.

Response: We agree with the reviewer’s opinion and have incorporated these considerations in abstract (page 2) and discussion (pages 8 and 9) of the revised manuscript.

6. Do the title and abstract accurately convey what has been found?
Yes

7. Is the writing acceptable?
Yes

In conclusion this paper reports the results of a surgical technique that may have important long-term benefits to patients however can only be described as a pilot study that needs formal analysis.

Response: This has been done in the revised manuscript (pages 9 and 10).

Reviewer’s report:
Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached) – please ensure that the discussion and conclusions further reflect the very preliminary nature of this report.
-please add more reference to the natural history of the aortic arch dimensions in such patients that just undergo aortic valve surgery.

Response: thank you for this comment – this has been incorporated into the revised manuscript.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer's report
Title: Aortic wrapping for mild to moderate ascending aorta dilatation is associated with early favourable aortic remodelling
Version: 1 Date: 5 April 2010
Reviewer: Ramesh Patel

Reviewer's report:
Aortic wrapping for mild to moderate ascending aorta dilatation is associated with early favourable aortic remodelling'
Keng-Leong Ang, Furqan Raheel, Amrita Bajaj, Andrzej Sosnowski and Manuel Galinanes
Journal of Cardiothoracic Surgery
Research article

When assessing the work, I have considered the following points:
1. Is the question posed by the authors new and well defined?
The question posed by the authors is new and not well defined
Response: We have made substantial changes to the revised manuscript following the reviewers’ comments to better define the reported preliminary study.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
The procedure is described well. What is not clear is on what basis was the size of the Dacron graft chosen (2.5 – 3.5cm). Was this on the BSA, % reduction, size of the “normal aorta” as determined from the CT scan or other method? In addition was the tube graft stretched or left crimped.
Response: The aim was to reduce the size of the ascending aorta to a diameter less that 3.5cm. The size and length of Dacron graft was determined by intra-operative measurements of aorta from the STJ to the origin of the brachiocephalic arterial trunk so that the graft can fix snugly around the aorta at the end of the procedure. These clarifications have now been incorporated to the revised manuscript (page 4, paragraph 2).

Three patients had CABG - were these all IMA grafts or SVG. If SVG how were the proximal anastamosis undertaken? The type of aorototomy undertaken (traverse vs hock-stick), is not mentioned.
Response: All 3 patients had SVG. The proximal end of the SVG of 1 patient was attached to the ascending aorta through a hole made in the Dacron graft. The
remaining 2 patients had their proximal SVG attached to the aorta distal to the Dacron graft. This comment has been inserted in the revised manuscript (pages 4 and 5).

Major Compulsory Revisions

3. Are the data sound and well controlled?

The data is not controlled. How can we be certain that the reverse remodelling that took place, in areas other than that was not wrapped, was not from correcting the aortic valve pathology by replacement of the valve? Is there any data for these measurements by the authors where the patients have undergone AVR in isolation? The authors could have addressed this by CT measurements in those patients in whom the wrap was not undertaken and had AsAo in their upper limits. No mention this as weakness/limitations of their study is made anywhere in their manuscript.

Response:

Similar concerns were made by another reviewer. We acknowledge that our study, although reporting interesting results, is a preliminary, pilot study that has no controls. Data on the natural history of mild-moderately dilated aorta following isolated AVR are scare. It is controversial whether AVR alone is sufficient to prevent further aortic dilatation. A greater risk of dissection and rupture following isolated AVR have been reported in these patients, hence there are recommendations that favour correction of the aorta at the time of primary aortic valve surgery. We recognise the limitation of our study that has been incorporated in the revised manuscript (page 9, paragraph 3).

It is of no surprise that the ascending aorta diameter is significantly reduced in size because it was wrapped! (Physically constricted!) One should expect this without question. The importance is the reduction in the STJ where there is reduction but with weak statistical significance. The possible explanation could be that weak reduction in STJ could be as a result of aortotomy closure and again from the wrap constricting the region. In the method, the wrap is described to start from the STJ.

The important question also arises is the reduction in the coronary sinus measurements, where there is reduction again with weak statistical significance. Could this have been from the correction of the aortic valve pathology? Only 3/14 patients had what seems an appreciable reduction in the sinuses dimension (Figure 1). Were these in whom AR was the isolated manifestation? The sinusus as well as AsAo and the arch is often noted to expansile in severe AR (wide pulse pressure) and could this be the reason for the discrepancy in the measurements pre to post AVR where post op there is no AR? The question also arises is the reduction in the aortic arch measurements, where there is reduction again with weak statistical significance. Again could this have been from the correction of the aortic valve pathology? 6/14 patients had what seems an appreciable reduction in the sinuses dimension (Figure 1). Were these in whom
again AR was the isolated manifestation?

Response: As previously pointed out, at present there is a lack of data in the literature to support that correction of aortic valve pathology alone is sufficient to “correct” mild-moderately aortic dilatation. However, it is important to note that the remodelling of the aorta proximal and distal to the wrapping was not dependent on the aortic valve pathology. We have now incorporated this in the revised manuscript (page 7).

There is uncertainty on the statistical testing. Surely the variables of dimensions were not normally distributed. Though mentioned - “Continuous variable that were normally distributed were presented as mean ± SD, and differences between groups were compared using paired t-tests”. The only data is the measurements It would seem that the authors have applied parametric testing for a discontinuous variable looking for a p value of <0.05!

Response: On statistical testing for normality, the variables for dimensions were normally distributed, and therefore it is correct that the differences between groups were compared using paired t-tests. We have discussed and confirmed with the Department of Statistics at the University of Leicester the correctness of the statistic method used in our study.

What was the blood pressure control in these patients at the time of their repeat CT measurements?

Response: Blood pressure was adequately controlled in all patients before and after surgery. This clarification has been inserted to the revised manuscript (page 6, paragraph 1).

In the period of time were any patients turned down from having the wrap?

Response: No, however, only the patients described have complete pre-op and post-op imaging fulfilling the study criteria.

- Major Compulsory Revisions

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

There is lack of information on the characteristics of patients operated upon.

Response: As requested, we have further elaborated the characteristics of patients operated in the revised manuscript (page 6 paragraph 1).

- Minor Essential Revisions

5. Are the discussion and conclusions well balanced and adequately supported by the data?

Line 4, page 7: The procedure can be performed within 5-10 minutes. This is an exaggerated statement for the reasons provided;

1) The ascending aorta along with the STJ and the arch to its some extent has to
be freed from the PA and pericardia reflections
2) Any bledders have to be ensured haemostatic.
3) Some form of measurements have to be performed
4) Correct graft size has to be opened and slit open
5) The correct length of the Dacron wrap has to be detrained
6) This has to be passed around the AsAo without crimping and placed snugly around the aorta
7) A vertical suture to approximate the split end is necessary.

Response: The procedure is of great simplicity, performed frequently in our unit and does not require an extended period of time to be accomplished. The dissection of the aorta is performed using diathermia and we have not encountered bleeding problems derived of the dissection; none of the patients were re-operated for this cause. Certainly, we can reassure to the reviewer that in our hands the procedure can be performed within a 10-minutes period.

The safety element is not tested in this report

Response: The procedure has been performed regularly in our unit and known to be safe. Therefore, in this study the aim was to look at the effect of the wrapping on remodelling of the aorta as the procedure was considered safe.

Line 3 page 7: All the patients in this study had their aortas opened.

To undertake this procedure in 14 patients and conclude there are no complications and to use the word “significance” is not at all scientific. No the discussion and conclusions are not balanced and do not adequately support the data.

Response: We have not observed complications derived from the procedure and we believe is safe. The word significance is used for the statistical analysis. To add “balance” to the manuscript, we have now incorporated all the suggested feedbacks, including the preliminary nature and the limitations of the study.

Line 9 page 7; “benefit seen as early in all areas within 2 weeks after surgery”
What were the timings of the post op CT. There is no data on early or late CT measurements.

Response: The CT scans were performed 4 weeks after surgery as indicated in the resubmitted manuscript (page 4, 1st paragraph) and therefore we have modified the sentence removing the specific time notation. Thanks for pointing out this inaccuracy.

Line 13 page 7: The word remodelling is incorrect. if any did take place, this has to be termed reverse remodelling.

Response: The reviewer is correct and therefore we have substituted the word remodelling by reversed remodelling through the manuscript. Thank you.
Line 14 page 7: Is it again due to correction of AV pathology or is it due to wrapping cannot be concluded.

Response: As mentioned above, the current literature suggests that AVR alone does not prevent further dilatation, especially if native aortic valve is bicuspid. Furthermore, there is a greater risk of dissection and rupture following AVR when the aorta is dilated. We are describing here an observation that has not been previously reported.

Line 14 page 7: Are the authors advocating the “wrapping” where there is no AV dysfunction?

Response: This point has been clarified in the revised manuscript (page 8, 2nd paragraph) indicating that the procedure is performed when associated to other cardiac surgical corrections, usually of the aortic valve. However, the observed reversibility changes could support the case for an early intervention in mild to moderate ascending aortic dilatation so that in addition to stopping its progression, the future abnormal dilatation in the remaining aorta can be prevented. Obviously, this has to be established by further study as the study is preliminary in nature (page 11, 3rd paragraph).

Last 2 lines page 7: Statements without admissions of data for scrutiny should not be made.

Response: Thank you for this feedback. We have now removed this and revised our manuscript accordingly.

- Major Compulsory Revisions

6. Do the title and abstract accurately convey what has been found?
NO. The title should include patients undergoing aortic valve replacement with associated aortic dilatation

The aorta has to be reserve remodelled. The aorta has dilated as a result of remodelling process due to the in this case aortic valve pathology. The authors should be refrained from confusing the terminology.

Response: We agree with the reviewer on these points and the title of the manuscript has been changed and the correct use of the term reversed remodelling has been adopted. Thanks.

- Minor Essential Revisions

7. Is the writing acceptable?
The grammar is correct.

However the authors are misinterpreting the law of Laplace. The law is a relationship of cavity dimension and wall stress.
In this case we could postulate:
Pressure in the aorta ($P$) = $2 \times$ aortic wall tension ($T$) / aortic luminal radius ($R$)
And from this we could postulate that the wall tension is increased as the dimension increases.

It has no baring to the adverse flow turbulence as mentioned in the manuscript (page 3 line 6). That is perhaps an entire different entity.

Response: Thanks for pointing this out. This has now been rephrased in the revised manuscript.

- Minor Essential Revisions
In conclusion It is my view that major compulsory revisions has to be made which the author must respond to before a decision on publication can be reached.

Confidential comments to editors
Comments that relate to ethical. This analysis though undertaken in retrospect had not sought for ethical approval. Concerns are that

1 Patients were subjected to experimental procedure without due ethical approval.
2 The consent process is not well described.
3 CT scans were performed pre, and more importantly post operatively with this procedure without mention in the manuscript of consent or ethical approval.
4 Is it the practice of the department to CT all aortas for AVR pre and post op and that as early as 2 weeks?
5 Was the procedure explained to patient that in future any reoperations would be faced with difficulties?
6 The prosthetic material may get infected, induce inflammatory response produce fibrosis.

Response: With respect to the reviewer’s first comment, aortic wrapping either alone or with other aortic reduction procedures are well established surgical techniques reported in the literature as early as 1991 (Carel et al Eur J Cardiothoracic Surg 1991, 5: 137-43; Robiscek F et al J Thoracic Cardiovasc Surg 2004, 128:562-70; Cohen et al Ann Thorac Surg 2007, 83: S780-4). Hence is not an experimental procedure. In the past, echocardiogram is used to monitor patient’s aortic dimensions. However, with the emergence of CT scanning as the standard of practice for aortic measurements, it is now our practice to perform CT scan for all aortas which are through to be dilated on echocardiogram or angiogram pre-operatively. CT scan is also our preferred clinical investigation modality for following-up our patients. The procedure, its risks (such as risk of prosthetic materials, future re-operations) and special follow-up arrangements were explained during the surgical consent process to the patients, like any other surgical procedures. 'The study was approved by the local Ethics Committee.
and, because this was a retrospective analysis of a procedure previous reported and of investigations performed as part of the standard care, patient's consent was not required. We have now clarified this in paragraph 3 of page 7.

This is my assessment of the manuscript and my advise should be that I am unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest
-----------------
I found the article interesting but lacked scientific rigour:
- An article of importance in its field

Quality of written English
- Acceptable

Statistical review
------------------
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.
- Yes, and I have assessed the statistics in my report.

Declaration of competing interests
----------------------------------
Please complete a declaration of competing interests, considering the following questions:
- Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? NO
- Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? NO
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? NO

Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? NO
- Do you have any other financial competing interests? NO
- Do you have any non-financial competing interests in relation to this paper? NO

'I declare that I have no competing interests'

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
None