Author's response to reviews

Title: Comparison of the Novel Medtentia Double Helix Mitral Annuloplasty System with the Carpentier-Edwards Physio Annuloplasty Ring: Morphological and Functional Long-Term Outcome in a Mitral Valve Insufficiency Sheep Model

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Version: 2 Date: 1 March 2013

Author's response to reviews: see over
Dear Sirs,

thank you very much for sending us the reviews of our paper! We were able to comply with nearly all requests of the reviewers and we feel that their input has improved this manuscript.

With best regards

Univ.-Prof. Dr. med. M. A. Konerding

**Reviewer’s report**

**Title:** Comparison of the Novel Medtentia Double Helix Mitral Annuloplasty System with the Carpentier-Edwards Physio Annuloplasty Ring: Morphological and Functional Long-Term Outcome in a Mitral Valve Insufficiency Sheep Model

**Version:** 1  **Date:** 1 January 2013  
**Reviewer:** Wolfgang Bothe

**Reviewer’s report:**

In this work the authors compared a novel mitral annuloplasty ring system to a CE Physio ring in a chronic large animal study. Primary outcome measures included macro- and microscopic findings surrounding the rings at the time of sacrifice (morphological outcomes) as well as functional outcomes such as implantation time, freedom from mitral regurgitation and LV dimensions.

First of all, the authors should be congratulated for having performed such a complex large animal study using a chronic model of functional mitral regurgitation.

Thank you very much!

I have, however, several concerns which mainly refer to the clarity of the manuscript.

1. Starting with the abstract: The terms ‘morphological and functional outcome’ are broad and it is not directly intuitive what the authors were aiming to investigate.

   **Text change:** This study was designed to examine the morphological and functional outcome of a new double helix mitral annuloplasty ring in an ovine model in comparison to the classical Carpentier-Edwards (CE) annuloplasty ring as measured by reduction of mitral regurgitation and tissue integration.

   The following methods section does not describe when and how the endpoints (which are not clear) were assessed (Echo? Histology? Timeline of the protocol?).

   **Text insertion concerning the endpoints:** Echocardiography for assessing mitral regurgitation as primary endpoint was done immediately before sacrifice. The annuloplasty rings with surrounding tissue were harvested for histological analyses as secondary endpoints.

   **Implantation time (p<0.01) and perfusion time (p<0.001) as clinical secondary endpoints**

   The times of sacrifice are given in the abstract.
Since the device used is almost unknown, both, a description of the device as well as of the method of implantation are needed.

Text insertion: The Medtentia annuloplasty ring (MAR) is a helical device that is rotated into the annulus enabling a simpler and faster fixation without the need of elaborate repair of the valve geometry. The ventricular part of the helical ring encircles the valve chords. Implantation was performed on-pump in a beating heart through the left atrial appendix.

Finally, authors draw conclusions that are not supported by their results. Was a ‘projected mitral valve area’ assessed (not described in any of the previous sections of the abstract)? If yes, how was it assessed and what were the results? And would it be valid to conclude that this novel device prevents mitral regurgitation by decreasing the orifice area?

Text change: Mitral valve regurgitation is effectively stopped both by restricting the pathological expansion of the annulus..

Comment: Mitral regurgitation occurs when the mitral valve does not close completely. The annuloplasty ring implantation aims on reducing or limiting the unnatural expansion of the annulus. The success can be measured by the clinical outcome in terms of reduction of regurgitation. Thus, the conclusion is valid even without measuring the valve area before implantation and after the observation time. This is discussed in the paper, however, due to the 350 word limitation we did not do that in the abstract.

With respect to the manuscript:

1. In the Methods section the implantation of the device should be described in more detail. It is not clear why the implantation of the novel device is faster than implanting a CE Physio if a similar number of sutures is placed.

Text insertion in the Introduction: Thus, there is no need for elaborate and time consuming valve reconstruction before fixation of the MAR.

Text insertion in the Discussion: … in order to meet the need for less complex, reproducible and fast repair techniques which may be added without further time delay to other heart procedures.

This is made possible by the helical construction principle that connects atrial and ventricular surface of the annulus and which restores the valve geometry by screwing in. Contrary to other annuloplasty systems the MAR needs stiches only for for fixation, while in conventional mitral rings the sewing oft he annulus to the ring prostheses is the active, more time consuming valve geometry repair step.

Were the animals randomized?

Text insertion in the Methods: The sheep were randomly assigned to the individual groups.
Why does one group consist of seven and the other of 13 animals?

Comment: This was explained a page later unter “Sampling”: The animals of the CE group and seven animals of the MAR group were sacrificed after 3.6 ± 0.3 months follow-up time. Of the remaining MAR group animals, two were sacrificed at seven, nine, and twelve months after annuloplasty.

Text insert in Study Groups: Seven sheep with MAR were intended for the direct comparison with animals with CE after 3.6 months, the remaining six MAR animals were intended for sampling at later time points.

2. In the Results section, MR grade, which is one of the fundamental parameters of this study, should be added to Figure 2.

Comment: The important results of the important mitral regurgitation grades are given in detail in the Result (“Induction of mitral valve insufficiency” and “Echocardiography”). We did not insert a graph or box plot for these results, since they were between both groups nearly identical.

This Figure should also be revised carefully with respect to formal errors (hidden legends, inappropriate boxes etc.).

Figure 2 was carefully revised and all superimposed elements were eliminated.

Fundamental surgical parameters should be emphasized (clamp time) [I guess this is the same like the perfusion time?] and less relevant parameters be deleted.

We deleted Figs. 2 c and d showing the "Total time of surgery" and the "Anesthesia time". The data are still mentioned in the text.

Furthermore, major parts of the Results section are not understandable. What does ‘Flno1’ or ‘Fl250237458’ mean and why is this relevant?

Sorry, the Reviewer is right: the animal designators or animal numbers are not relevant and were deleted.

No conclusions should be drawn in this part of the manuscript and this section needs to be more clear, concise and should focus on the most relevant findings.

Conclusions such as “thus demonstrating the feasibility of the MAR system as far as the time needed is concerned (Fig. 2e, f)” or “confirming the functional efficacy of the MAR system in comparison to the CE annuloplasty system” were eliminated and the text was improved.

4. In the Discussion section, attention must be paid that all conclusions are supported by the data presented.

This was improved by text changes, too.

Currently some parts of the manuscript sound more like wishful thinking rather than a
scientific article.

see above

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

The manuscript was revised by a native speaker (PD Dr. Debrah Bickes-Kelleher)

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests.

**Reviewer's report**

**Title:** Comparison of the Novel Medtentia Double Helix Mitral Annuloplasty System with the Carpentier-Edwards Physio Annuloplasty Ring: Morphological and Functional Long-Term Outcome in a Mitral Valve Insufficiency Sheep Model

**Version:** 1  **Date:** 23 January 2013

**Reviewer:** Namsik Chung

**Reviewer's report:**

<Major Compulsory Revisions>

1) Are there any compelling requirements for the new double helix system in patients with mitral insufficiency? Please clarify why this new system was developed and how it fulfilled preexisting unmet needs.

Text insertion in Intro and Discussion: … in order to meet the need for less complex, reproducible and fast repair techniques which may be added without further time delay to other heart procedures.

This ovine study has demonstrated that the MAR system may be implanted in a significantly shorter time than the well-proven CE annuloplasty ring enabling a shortening of additional clamp time in critical or combined disease patients. This is made possible by the helical construction principle that connects atrial and ventricular surface of the annulus and which restores the valve geometry by screwing in the double helical device. Contrary to other annuloplasty systems the MAR needs stiches only for fixation, while in conventional mitral rings the sewing of the annulus to the ring prosthesis is the active, more time consuming valve geometry repair step.

2) Time for surgery, perfusion time, and total implantation time is operator dependent variable. It should be clarified how the study was designed to overcome the operator dependency. [I thought that all implantations were done by the same team?]
The reviewer's assumption is correct. We inserted the phrase in the M&M section: All implantations were done by the same team in order to overcome operator dependency.

3) Any figures after the Medtentia annuloplasty double helix system implantation with TTEs might be helpful.

Comment: The authors decided not to insert these figures since they did not contribute to a better understanding of the results.

4) Although there were no clinical thromboembolic events, unevaluated subclinical thromboembolism in the animal study could be their limitations.

Comment: This is correct. On the other hand, if no clinical thromboembolic events were recorded and if histology did not show any signs of thrombotic events, subclinical thromboembolism is unlikely.

<Minor Essential Revisions>
1) 11 page: hromboembolic -> thromboembolic

All typos were corrected

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.