Author's response to reviews

Title: Morphological macrovascular alterations in complex regional pain syndrome type I demonstrated by increased intima-media thickness

Authors:

Nicola Derenthal (nicola.derenthal@rub.de)
Tim Maecken (tim.maecken@rub.de)
Elena Krumova (Elena.Krumova@rub.de)
Alfried Germing (Alfried.Germing@rub.de)
Christoph Maier (Christoph.Maier@rub.de)

Version: 2 Date: 19 December 2012

Author's response to reviews: see over
Object: MS: 1385918231799384- Morphological macrovascular alterations in CRPS demonstrated by increased intima-media thickness. Derenthal et al.

Dear Editorial Team,

Thank you very much for your reply. We are grateful to you and the reviewer for the helpful and constructive recommendations. We are glad that you appreciate our study and have revised the manuscript according to your comments. The modifications of our manuscript are underlined and highlighted by using red font to allow for easy recognition.

We hope that we have met all the points raised by the reviewers satisfactorily. Otherwise we would be glad to revise the manuscript according to any remaining comments and questions of the reviewers.

Sincerely yours

Prof. Dr. C. Maier
Reviewer's report

Title: Morphological macrovascular alterations in CRPS demonstrated by increased intima-media thickness

Version: 1 Date: 21 October 2012

Reviewer: Frank Huygen

Reviewer's report:
I reviewed an article entitled "Morphological macrovascular alterations in CRPS demonstrated by increased intima-media thickness”
The article is sufficiently novel and interesting. The title is clearly describing the content of the article. The structure is clear. The aim of the study is clear. There is an adequate abstract and introduction. The methods are appropriate and well described. The results are presented in a clear way. Discussion is well balanced and adequate. The limitations of the work are clearly stated. Referrals’ are adequate. The authors clearly acknowledge the work upon they are building. The English writing is adequate.
I would advice this article for acceptation. There are just a few remarks to be made (minor essential revisions):

Minor essential revisions:

In the background session the authors speak about sings, despite the fact that this is a typo I think it is better to speak about signs and symptoms. Pain is a symptom, not a sign.
  We agree with the reviewer and it has been changed as the reviewer indicates (page 5, line 8 and 10).

The authors selected CRPS patients by making use of the Budapest criteria. Can they specify either they made use of the research or clinical criteria.
  Thank you for this remark. We have specified that we selected CRPS patients by making use of the clinical Budapest criteria (page 7, line 13-16).

In paragraph 2.2 the authors speak about constricted, I would say restricted or limited.
  We have changed constricted into restricted (page 9, line 20).

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

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

Declaration of competing interests: None
Reviewer's report

Title: Morphological macrovascular alterations in CRPS demonstrated by increased intima-media thickness

Version: 1 Date: 20 November 2012

Reviewer: Floris Schreuder

Reviewer's report:
Derenthal and co-workers have written an appealing article in which they study the intima-media thickness (IMT) in various arteries in patients with type I complex regional pain syndrome (CRPS). The paper is well-formulated, original and relevant. As the authors state, there has not been any previous reports concerning macrovascular changes established by IMT in CRPS. The authors demonstrate that CRPS leads to locally increased IMT, with what it seems a gradient from proximal to distal in the affected hand. They suggest that this is due to previously demonstrated involvement of local inflammatory processes, which have been shown to alter the vessel wall in other diseases such as rheumatoid arthritis. As mentioned in the discussion, they cannot conclude that this observation is due to the supposed inflammatory responses since these were not measured in the present study. In addition, one major confounder is a difference in disease duration between the subgroups. A large point of concern and a possible large confounder may be the fact that the measurements were performed whilst the sonographer was not blinded to the clinical information. The authors should consider the following points:

- Major Compulsory Revisions

1/ In the discussion, please stress the fact and explain more detailed that it concerns a local process through which CRPS leads to macrovascular changes (i.e. no increase of CCA-IMT, gradient in the arm towards the hand).
   Thank you for this remark. We agree with this comment and we have added three sentences to the discussion (page 16-17, line 19-3).

2/ Rephrase the abstracts conclusion to exclude “acute phase of CRPS” since the mean duration of symptoms was 16 months according to table 1. Formulate the conclusion in two sentences. In the first, state your conclusion drawn from the findings. In the second sentence, discuss these findings in relation to what is known from the literature.
   We have rephrased the abstract as the reviewer indicates (page 4, line 4-7).

3/ Introduction, second paragraph: include a statement that IMT does not necessarily reflect pathological changing but is largely influenced by increasing age. This is important and should also be mentioned in the discussion, e.g. state whether the subgroups have different ages or not.
   Thank you for this remark. We have added one sentence on this issue in the introduction (page 6, line 4-5) and further two sentences in the discussion (page 15, line 13-17).
4/ Materials and methods: section 2.1: this subparagraph needs to be rewritten since it is very unclear. Start with specifying how CRPS patients were included in the study, including how the diagnosis of CRPS was made and by whom (not specified in the text at all). What is the number of patients initially studied. Next, what were exclusion criteria. How many patients were evaluated, and how many of these were not included after all (for instance the impossibility to complete the ultrasound examination due to pain). Then specify in a new paragraph how the control groups were included and evaluated (for the peripheral nerve injury group and lastly for the pain free controls). How was the diagnosis of peripheral nerve injury made (what EMG cut-off values, what clinical symptoms). The last sentence of this section raises a lot of questions: is only the dominant hand studied in the CRPS patients? If so, why is this? Is this also the case for the peripheral nerve injury group? Clearly state that the measurements were not blinded to clinical information as you specify in the discussion.

We agree with the reviewer and have rewritten the section 2.1 according to the reviewer’s suggestions (page 7-9). We have also added one citation ([20]) and an additive table (table 2, page 32). We would leave the decision to the editor whether this table should be included in the manuscript or in a supplement.

5/ Section 2.2.1: please specify measurement of the brachial and radial artery, which probe, which position, which position of the arm, etc.

We have specified measurements of the brachial and radial artery by adding five sentences (page 10-11).

6/ Please explain in discussion the difference in disease duration between CRPS and peripheral nerve injury patients since this may be a very important confounder.

Thank you for this remark. We have now explained in the discussion the difference in disease duration between CRPS and PNI patients by including three sentences (page 18, line 6-11).

7/ Follow the same order in the result section as outlined in the materials and method section: start with demographic data, next discuss CCA-IMT, next BA-IMT, RA-IMT, introduce Q-RA/CCA-IMT.

We have now followed the same order in the result section as outlined in the materials and method section (page 12-14).

8/ Result section: mention all measured numbers in the text, so that the tables are not necessary to be read (they might even be abolished). For instance, section 3.2: “Mean brachial IMT (BRA-IMT) was significantly increased on the affected side only in CRPS patients compared to PFC (0.42 ± 0.06 vs. 0.40 ± 0.08; p-value…).

We have now included all measured numbers in the result section (page 12-14).

9/ Remove in section 3.2 and 3.3 the correlations between the arteries since its irrelevant to the present study and is largely caused by IMT influenced by effects such as age.

We agree with this remark and have removed the correlations between the arteries in section 3.2 and 3.3.
10/ Please explain why a subgroup analysis was made of the median nerve injury patients: remember that you have extremely small subgroups. The difference is more likely due to chance than it is a real observation. In addition, it is not used in the discussion and the minute difference between ulnar and median nerve patients approaches the technical limitations of ultrasonographic devices.

   Thank you for this remark, we agree with the reviewer. Due to the small subgroups and technical limitations we have decided to remove this section about the subgroup analysis in the results and discussion.

11/ Please specify the effect of disease duration on all of the parameters studied in all subgroups.

   Thank you for this remark. We have specified the effect of disease duration in section 3.6 by displaying the effect not only on the RA-IMT but also on the CCA- and BRA-IMT in the CRPS and PNI group (page 14, line 5-8). This is also included in the discussion (please see point 6/).

12/ Rewrite the conclusion since it is now too bold to fit the data. Make no such strong mention of the relation between inflammation and locally increased IMT in CRPS, since the study design is not capable of demonstrating such a correlation.

   Thank you for this remark. We agree with the reviewer and have rewritten the conclusion by excluding the statement on increased IMT “probably resulting from … inflammatory processes” (page 20).

- Minor Essential Revisions

1/ Please remove the abbreviation CRPS from the title and specify that it concerns type I.

   The title of the article has been changed as the reviewer indicates.

2/ Rewrite the abstract to make it more readable (i.e. consistently use two decimal places; specify values according to artery, then patient group, then side; specify p-values).

   Thank you for this remark. We have rewritten the result section of the abstract and hope that it is now more readable (page 3-4).

3/ Introduction, second sentence: correct sings into signs.

   We have corrected the manuscript accordingly.

4/ Introduction, tenth sentence: …levels of proinflammatory… correct to pro-inflammatory.

   We have corrected the wording accordingly.

5/ Section 2.2: please specify inter- and intra-observer agreement for the study sonographer compared to the experienced sonographer.

   Thank you for this remark. We have added two sentences to specify inter-and intra-observer agreement (page 9-10, line 20-2).

6/ Section 2.2.1: please make sure the IMT is normally distributed. If so, write this down. If not, use medians +/- interquartile range instead of mean +/- SD.
Thank you for this remark. We have added that the IMT values were normally distributed (page 11).

7/ Section 2.3: make sure that for all values there is a normal distribution before using means +/- SD and corresponding statistical tests. Why are the associations tested between quantitative values as stated in last sentence?

Thank you for this remark. We made sure that all values are normally distributed by using the Shapiro-Wilks W-Test before using means ±SD and corresponding statistical tests. The last sentence of the section was mistaken so that we have rephrased it (page 11-12, line 21-2).

8/ Remove from discussion the sentences starting with “Myredal stated ...” to “atherosclerotic disease” since it is not relevant.

We agree with the reviewer and the sentences were removed from the discussion.

9/ In the discussion, the authors suggest that the findings are the result of both a systemic as well as a local inflammation process. Explain in more detail how the CCA is not influenced while the BA is only on the affected side.

Thank you for this remark. Please see our answer in point 1/ (Major Compulsory Revisions).

10/ Table 1: correct the percentages of genders per subgroup; remove median and range if normal distribution, please explain how someone in the peripheral nerve injury group can have a maximal pain intensity of 1 while the current pain level is 2.

We have corrected the percentages of genders per subgroup. We have removed median and range if normal distribution except from the range of the pain duration because in our view it is a very important information which is also mentioned in the discussion. It was a typo in writing that someone could have a maximal pain intensity of 1 while current pain level is 2. The maximal pain intensity was 2.

11/ Change the order of the legends of tables and figures accordingly: Values mean +/- SD. Percentages explained. P-values explained. Abbreviations explained. References to footnote (e.g. in table 1: multiple answers possible).

We have changed the order of the legends of tables and figures as the reviewer indicates.

- Discretionary Revisions

1/ The authors might consider removing table 2 and 3 since most of the values have been specified in the text and figures 1-3.

Thank you for this remark. We have added one table (table 2) in section 2.1 so that table 2 and 3 became table 3 and 4. We agree with the reviewer that most of the values have been specified in the text but for clearness reason we think table 3 and 4 are a reasonable addition. We would leave the decision to the editor whether these tables should be included in the manuscript or in a supplement.

2/ In the discussion, the authors could specify how they intend to do a more
extensive study to elucidate the questions that the present study has arisen, e.g. longitudinal ultrasound follow-up starting early after symptoms of CRPS have started with simultaneously measurements of inflammatory markers. In addition, one could provide a hint of a new study confirming the finding of locally enlarged IMT in peripheral nerve injury patients.

Thank you for this remark. We agree to the reviewer and we have added two sentences to the discussion (page 19, line 10-11 and line 18-21).

Level of interest: An article of importance in its field

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.

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