Author’s response to reviews

Title: Contrast enhanced transesophageal echocardiography in patients with atrial fibrillation referred to electrical cardioversion improves atrial thrombus detection and may reduce associated thrombembolic events

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Author’s response to reviews: see over
To the Editors in Chief
Prof. Eugenio Picano
Prof. Rosa Sicari

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Revised Manuscript: “Contrast enhanced transesophageal echocardiography in patients with atrial fibrillation referred to electrical cardioversion improves atrial thrombus detection and may reduce associated thrombembolic events“

Dear Professor Picano,

Thank you for the important revisions of the above mentioned manuscript, which we overworked substantially according to the reviewers comments and hope that the manuscript will now comply with the standards of the Journal. The answers to the reviewers’ comments and all changes are listed in detail in the attachment to this letter.

We would like to ask you to consider the revised manuscript for publication.

With best regards,

Philip Jung, M.D.
Response to reviewer 1:

Major compulsory revisions:

1. The abstract was shortened from 420 words to 402 words, especially in the sections ‘Aims’ and ‘Methods’

2. The text was changed, since patients who were deemed eligible for CV from our cardiological point of view could have contraindications such as other clinically important conditions.
   previous version: “.. 180 consecutive patients with AF and planned CV were randomized..”
   revised text: “..180 consecutive patients with AF and indication for CV were randomized..”

3. The remaining patients were those that were not deemed eligible for CV, especially because of thrombus detection or inconclusive results. The text was changed accordingly to clarify this:
   previous version: “..In the remaining patients anticoagulation was started..”
   revised text: “..In the remaining patients, i.e. those not suitable for CV, anticoagulation was started..”

4. In case of disagreement consensus was sought and achieved in every instance in a second joint session of both observers. This explanation was added to the methods section in the text.

5. The major intention of the study was to compare both imaging methods, which were applied only to group 1. Therefore, the more detailed assessment of the interpretability of the images was only applied in group 1. Therefore, the exact number of patients with inconclusive readings is not known. However, group 1 comprises 90 patients and the comparison of interpretability between native and contrast enhanced imaging in this group yielded highly significant results. Furthermore the number of subsequently cardioverted patients is almost equal in both groups suggesting a similar rate of interpretable and non interpretable images.

6. As recommended by the European Heart Rhythm Association success of CV was defined as the documentation of at least one beat in sinus rhythm. Accordingly the success rate was 94.6% in group 1 (70/74 successful cardioversions) and 92.1% in the control group (71/76 successful cardioversions). The following text was added in the results section:
   “The success rate of CV was 94.6% in group 1 (70/74 successful CV) and 92.1% in the control group (71/76 successful CV, p=0.73).”

7. Movie clips would be more meaningful. However, the provided images represent good and typical examples of native and contrast enhanced images and document well the difference in interpretability.
Minor compulsory revisions:
1. A native English speaker read and revised the paper.
2. The error was corrected: “thrombus” instead of “thromubs” and “non conclusive” instead of “non onclusive”
Response to reviewer 2:

Major issues:

1. The groups were formed in a randomized way within the same time period. However, due to the observational design of the study there was no independent randomisation. Nonetheless, both groups showed no significant differences regarding the baseline characteristics, percentage of eligibility for CV and success rate of CV. According to this important comment, the following text was added in the methods section:
   “..were randomized by the investigators within the same study period to..”

2. The protocol for the application of the contrast agent was standardized. To clarify this, the underlined text was added:
   “..bolus of 1ml contrast agent (SonoVue™ Bracco Diagnostics Inc., Princeton, NJ, USA) into an antecubital vein followed by a bolus of 5-10ml saline according to our standardized study protocol.”
   The randomization of the patients to group 1 or the control group was independent of the native image quality.

3. It is already stated in the results section, that no relevant adverse events regarding the administration of the contrast agents were observed. One vial of the contrast agent costs about 70€ in our institution and is sufficient for 2-3 patients. We feel that this additional expense is acceptable compared to the serious sequelae of non detected atrial thrombi and subsequent thromboembolism. However, the cost effectiveness of contrast enhanced TEE should be studied and discussed in a separate manuscript.

Minor issues:

The manuscript was read and revised by a native English speaker.

References and citations were formatted according to the rules of the journal.