Author's response to reviews

Title: Effect of Remote Ischemic Conditioning on atrial fibrillation and Outcome after coronary artery bypass grafting (RICO-trial)

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Version: 2 Date: 8 April 2011

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

Thank you for reviewing the manuscript entitled: “Effect of Remote Ischemic Conditioning on atrial fibrillation and Outcome after coronary artery bypass grafting (RICO-trial). We would like to respond to the questions and concerns posted by the reviewer:

Reviewers comment:
1. The question is if it should be better defined what pressure will be achieved in the cuff, if exactly the same pressure will be held throughout the procedure (is this possible with an automatic inflator cuff?) and how ischemia in the arm will be determined.

Response:
We stated that we would use an automatic inflator cuff to induce arm ischemia. We reworded this phrase as we will use surgical tourniquets, which will be inflated to 200 mmHg for conditioning. There is a monometer measuring pressure within the cuff, allowing to control that constant pressure is applied during arm ischemia. These devices are designed to induce bloodlessness, and thereby ischemia, e.g. for orthopedic surgery.

Reviewers comment:
2. A minor point is the induction of anesthesia. Since propofol is used for maintenance of anesthesia why is it not used for induction. Midazolam seems to be a rather unusual choice for an induction agent, as deep anesthesia cannot be achieved. Will a measure of anesthetic depth be used?

Response:

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For the induction of anaesthesia midazolam and/or propofol is used, along with opioids, depending on the anaesthesiologist’s preference. Maintenance will be done using propofol and opioids, which is a common method for maintenance in cardiac surgery. This has been corrected in the manuscript.

**Reviewers comment:**

3. *In the statistical analysis it is not explained why a reduction of 45% in afib is clinically relevant in the single conditioning groups and why a reduction of 60% in the combined group. This should be stated more clearly.*

**Response:**

We agree that we made some assumptions to allow power calculation. A relative reduction in the occurrence of atrial fibrillation of 40-50% by either pre- or postconditioning seems reasonable and clinically relevant. This number was used to calculate the group size in groups with single intervention. However, for a combined intervention of pre- and postconditioning, the effect should be stronger, to justify the extra effort. If the combined intervention would produce a reduction similar to that we expect to see in the preconditioning or postconditioning groups, there would be no added value of combing both interventions. Therefore, in the pre- and postconditioning group, we only consider an even higher reduction of post-operative atrial fibrillation clinically relevant, in this case 60%.

The revised manuscript will be uploaded together with this letter.

Yours sincerely,

Benedikt Preckel, MD, MA, DEAA