PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Influence of pre-infarction angina and coronary collateral blood flow on the efficacy of remote ischaemic conditioning in patients with ST-segment elevation myocardial infarction: post-hoc subgroup analysis of a randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Pryds, Kasper; Bøttcher, Morten; Sloth, Astrid; Munk, Kim; Schmidt, Michael; Botker, Hans Erik</td>
</tr>
</tbody>
</table>

GENERAL COMMENTS

The present paper presents a retrospective analysis of the original CONDI trial (ref. 4) and addresses the potentially confounding influence of pre-infarction angina within 3 months before the index event (medical records) and angiographically visible collaterals (Rentrop score) on the effectiveness of a remote ischemic preconditioning (RIC) manoeuvre (4 cycles of 5 min upper arm ischemia/5 min reperfusion) on myocardial salvage index (SPECT). Pre-infarction angina had no effect on protection by RIC, whereas salvage by RIC was greater in patients with collateral blood flow. The authors adequately acknowledge the limitation of their retrospective subgroup analysis, but nevertheless provide on an exploratory level novel and important information.

I have only minor issues to suggest for revision:
P11, l16: here you may want to add to ref. 13 Circulation 103, 2001, 2876-8.

GENERAL COMMENTS

Dr Pryds and co-worker performed an explorative post-hoc analysis of the Prof. Botker original manuscript published in Lancet 2010. The aim of the present analysis was to assess if pre-infarction angina or coronary collateral blood flow could act as outcome modifier of RIC on myocardial salvage index (SPECT based). Overall the manuscript is well written and add important knowledge on the elusive mechanism of RIC. Of note authors demonstrate that CCBF may increase RIC effect thus supporting circulating mediator of cardio-protective effect. This also imply that remote...
ischemia/reperfusion cycles may need to be prolonged until TIMI 3 flow is obtained in future trials. In this revision the authors addressed well all reviewers’ comments. My only concern regards lack of interaction test; p for interaction either crude or confounder adjusted, should be provided using linear regression according to the models below:

\[ MSI = RIC \times CCBF \]
\[ MSI = RIC \times Pre-Angina \]
\[ MSI = RIC \times CCBF + \text{Confoundersn} \]
\[ MSI = RIC \times Pre-Angina + \text{Confoundersn} \]

Also I believe that CCBF Rentop grade should not be included as a continuous variable in a linear regression but “dummy variables” should be used instead, this imply also a revision of Figure 4. Please double check all CI, I guess these express CI for difference in means, please and specify.

### VERSION 1 – AUTHOR RESPONSE

Reviewer Name
Gerd Heusch

Institution and Country
Institute for Pathophysiology, West German Heart and Vascular Center, University of Essen Medical School

Please state any competing interests or state „None declared“: none declared

Please leave your comments for the authors below

The present paper presents a retrospective analysis of the original CONDI trial (ref. 4) and addresses the potentially confounding influence of pre-infarction angina within 3 months before the index event (medical records) and angiographically visible collaterals (Rentrop score) on the effectiveness of a remote ischemic preconditioning (RIC) manoeuvre (4 cycles of 5 min upper arm ischemia/5 min reperfusion) on myocardial salvage index (SPECT). Pre-infarction angina had no effect on protection by RIC, whereas salvage by RIC was greater in patients with collateral blood flow.

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P11, l16: here you may want to add to ref. 13 Circulation 103, 2001, 2876-8.

Answer: We truly appreciate the thorough review and reflections upon our manuscript, and that the reviewer finds that the manuscript provides novel and important exploratory information.

We emphasize that in the present manuscript, we assessed pre-infarction angina occurrence within 48 hours before the onset of ST-segment elevation myocardial infarction and not 3 months.

We agree that the proposed references are highly relevant for our manuscript and have included Circulation 2001;103:2876-8 and Pharmacol Rev 2014;66:1142-71 as references on page 11 in the revised manuscript.
Dr Pryds and co-worker performed an explorative post-hoc analysis of the Prof. Botker original manuscript published in Lancet 2010. The aim of the present analysis was to assess if pre-infarction angina or coronary collateral blood flow could act as outcome modifier of RIC on myocardial salvage index (SPECT based).

Overall the manuscript is well written and add important knowledge on the elusive mechanism of RIC. Of note authors demonstrate that CCBF may increase RIC effect thus supporting circulating mediator of cardio-protective effect. This also imply that remote ischemia/reperfusion cycles may need to be prolonged until TIMI 3 flow is obtained in future trials.

In this revision the authors addressed well all reviewers’ comments. My only concern regards lack of interaction test; p for interaction either crude or confounder adjusted, should be provided using linear regression according to the models below:

\[
\begin{align*}
\text{MSI} &= \text{RIC} \times \text{CCBF} \\
\text{MSI} &= \text{RIC} \times \text{Pre-Angina} \\
\text{MSI} &= \text{RIC} \times \text{CCBF} + \text{Confounders} \\
\text{MSI} &= \text{RIC} \times \text{Pre-Angina} + \text{Confounders}
\end{align*}
\]

Answer: We truly appreciate the thorough review and reflections upon our work, and that the reviewer finds that the manuscript is well written and adds important information on the mechanism of remote ischaemic conditioning.

We agree that test for interaction should be used for subgroup analysis. Already in the initial submission, we tested for crude effect modification, i.e. interaction test, using the same linear regression model as proposed by the reviewer. However, we agree that this may not have been sufficiently specified in the initial manuscript. Consequently, we have highlighted this important consideration on page 7 in the “Statistical analysis” section and on page 9-10 in the “Results” section in the revised manuscript. As proposed by the reviewer, we have also included interaction test with adjustment for potential confounding effects.

Also I believe that CCBF Rentop grade should not be included as a continuous variable in a linear regression but “dummy variables” should be used instead, this imply also a revision of Figure 4.

Answer: We agree that it may have been incorrect to include the Rentrop score as a continuous variable in a linear regression model. We sought to investigate whether the degree of coronary collateral blood flow, i.e. the Rentrop score, to the infarct-related artery influences on myocardial salvage index. Consequently, as proposed by the reviewer, we have treated the Rentrop score as an ordinal variable in the revised manuscript, and performed Spearman’s rank correlation analysis to evaluate whether the Rentrop score influences on myocardial salvage index in patients treated with primary percutaneous coronary intervention alone or remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. We have highlighted these important considerations.
on page 7-8 and 11, and revised Figure 4 accordingly.

Please double check all CI, I guess these express CI for difference in means, please and specify.

Answer: We agree that the use of 95% confidence intervals may not have been sufficiently specified in the initial manuscript. For Student’s t-test analysis, data are presented as mean (standard deviation) with 95% confidence interval for the difference in mean. For linear regression analyses, data are presented as regression coefficient with 95% confidence interval for the regression coefficient. We have highlighted this important consideration on page 8 in the revised manuscript.
Influence of preinfarction angina and coronary collateral blood flow on the efficacy of remote ischaemic conditioning in patients with ST segment elevation myocardial infarction: post hoc subgroup analysis of a randomised controlled trial

Kasper Pryds, Morten Bøttcher, Astrid Drivsholm Sloth, Kim Munk, Michael Rahbek Schmidt and Hans Erik Bøtker

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