Author's response to reviews

Title: Passive Tobacco Exposure Impairs Symptomatic Improvement in Patients with Chronic Angina Undergoing Enhanced External Counterpulsation

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Author's response to reviews: see over
July 17, 2008

Iratxe Puebla
Senior Assistant Editor, *BMC Cardiovascular Disorders*

**Re: Revised MS 5352894041543196**

Dear Iratxe Puebla:

On behalf of the co-authors, I would like to submit this revised original research manuscript entitled "Passive Tobacco Exposure Impairs Symptomatic Improvement in Patients with Chronic Angina Undergoing Enhanced External Counterpulsation" for consideration for publication in *BMC Cardiovascular Disorders*. Changes in the manuscript were identified using red font.

We have revised the manuscript in response to each of the comments by the three Reviewers:

**Reviewer #1:** Authors have adequately addressed my comments.

**Reviewer #2:** The paper is unacceptable, the reviewers have not incorporated the standard statistical recommendations, and therefore makes the inferences unacceptable. The reviewers have made no attempts to incorporate any of the suggestions.
Response: We respectfully disagree with each of the “statistical analysis” recommendations made by Dr. Arora. This manuscript focused on the subgroup of those subjects with second-hand smoke exposure. We do not agree with Dr. Arora’s recommendation for pre-specified and post hoc subgroup analyses, assessing the impact of type I errors, assessment of treatment effects heterogeneity, and inclusion of a forest plot. None of these issues were raised by Reviewer #3. As the authors and Reviewer #3 do not believe these are valid statistical issues, we will not include them in this manuscript.

We are pleased that the Editors have sought a third Review, which is very reasonable. We have made considerable improvements in the manuscript in response to each of Reviewer #3’s comments.

**Reviewer #3:**
1. General Why did the authors choose to report this particular endpoint, improvement in anginal class, over, for example, reduced use of anti-anginal medication, or QOL indices? What were the results of these measures between the two groups?
Response: This endpoint has been used in majority of the previous publications evaluating the effectiveness of EECP therapy, so it is useful for comparison purposes. All patients have angina class reported. Anti-anginal medication dosage information pre- and post treatment was not part of the data collected.
2. The authors need to give the definition of “non-smoker” that was used for the registry. A limitation of concern is the reliability of self-report, especially if the subject claims to have quit but is living with a smoker. How certain are the authors that the effect is really SHS and not direct smoking in patients who simply are trying to avoid a "lecture" about the hazards of smoking? It may be helpful to report the percentage of never smokers and former smokers and to assess whether the EECP effect is different in them in the presence of SHS.

Response: The definition was added to page 6: Non-smoking is defined as no current tobacco smoking, by self-report. The proportion of former smokers in this group is listed in Table 1. There was no difference in outcome between the non-smokers and previous smokers exposed to SHS. The majority of the cohort report prior smoking.

3. Page 6, Statistical analysis "Changes in continuous variables were analyzed by paired t-tests." I don't think such analyses needed to be performed. Two-sample tests of continuous variables were apparently performed, and the authors should comment on the test used (e.g. unpaired t-test, rank sum test...).

Response: The statistical methodology paragraph has been rewritten and corrected to further elaborate the statistical tests used.

4. Page 6, Statistical analysis Angina class is an ordinal variable and should be tested with either a Mann-Whitney rank sum test or an Armitage trend test to account for the ordered nature of its categories. The test chosen should be noted.

Response: See above point 3.

5. Page 6, Statistical analysis "Multivariate logistic regression..." Please use either "Multivariable logistic regression" or "Multiple logistic regression" consistently throughout the paper. These terms refers to multiple explanatory variables, where as "multivariate" analyses technically refers to the analysis of multiple dependant variables.

Response: Thank you for this comment. The notation has been changed to multivariable logistic regression throughout the revised manuscript.

6. Page 6, Statistical analysis "Multivariate logistic regression modeling to predict failure to improve anginal status was performed." It is here that the authors should comment on how variables were screened and selected for the model. Were non-linear associations between continuous variables and the endpoint inspected and modeled?

Response: The modeling methodology has been expanded. In the model, there was a non-linear association with age. When age was dichotomized at 55 years, the model performed appropriately using statistical testing.

7. Page 6, Statistical analysis Presumably some patients died on follow-up. How were they handled for the analysis of the primary endpoint? If no patients died on follow-up, this should be stated in the results.

Response: As is shown in Table 3, some patients died during or shortly after the treatment period. Their last angina status, if reported, was used in the analysis.

8. Page 6, Statistical analysis Presumably some data values were missing? What was the extent of missingness and how was it handled in the analyses, especially the multiple
regression model.
Response: The revised statistical methods section covers this important area. The proportions and means reported here are calculated from patients who had this data recorded.

9. Tables and Results In the tables and text, report actual p-values rather than "NS", "p<0.05", and "p<0.01". The p-values have been calculated -there is no reason to keep them from the reader. Report p-values>=0.10 to two significant digits, p-values<0.10 to three significant digits.
Response: The p-values have been added to the abstract, text, and tables.

10. Figure 1 The figures leave something to be desired. The lone figure is essentially a plot of three numbers. I recommend the following: a) Would like to see a plot of the changes in anginal class for SHS and non-SHS non-smokers. Here is an idea of what may be revealing, though the authors are welcome to entertain other approaches: create a bar plot with a bar for each SHS group/baseline anginal class combination. The bar spans an axis from 0 to 100 and is broken and colored within according to the post-treatment anginal class percentages. This way the reader could see how the distribution of post-treatment anginal class for patients with a pre-treatment class of IV varies by SHS group. The authors may have to combine the I/II pre-treatment classes. b) Another useful plot would be simply a bar plot of post-EECP anginal class for the the three groups.
Response: Thank you for this comment. This figure has been replaced. Our revised figure shows the distribution of angina class for each of the analysis groups both pre- and post-EECP treatment.

11. Page 8, 1st para. The authors should present the entire model results, not just the estimates for those variables that were statistically significant. Also, completion of EECP treatment should not be in the model. When the physician is trying to assess whether a patient is a good candidate for EECP, they cannot know for certain whether the patient will complete the treatment. Further, if SHS does reduce the efficacy of EECP, then SHS patients are probably less likely to complete treatment due to dissatisfaction with symptom relief -meaning that failure to complete is more of a treatment outcome itself than a treatment choice. Including this as a predictor is likely "blocking" significant associations of true baseline variables with the outcome.
Response: The comments regarding the use of ‘completion of EECP’ are well taken. The model has been reanalyzed. The complete preliminary model is

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.7975</td>
<td>0.6860</td>
<td>1.3512</td>
<td>0.2451</td>
</tr>
<tr>
<td>SHS</td>
<td>0.6745</td>
<td>0.2366</td>
<td>8.1291</td>
<td>0.0044</td>
</tr>
<tr>
<td>Age (per yr)</td>
<td>-0.0187</td>
<td>0.00765</td>
<td>5.9585</td>
<td>0.0146</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>0.0157</td>
<td>0.3063</td>
<td>0.0026</td>
<td>0.9592</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>-0.1856</td>
<td>0.3081</td>
<td>0.3628</td>
<td>0.5469</td>
</tr>
<tr>
<td>Past smoking</td>
<td>-0.00355</td>
<td>0.1701</td>
<td>0.0004</td>
<td>0.9834</td>
</tr>
<tr>
<td>Class III/IV</td>
<td>-1.0076</td>
<td>0.2801</td>
<td>12.9415</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.0315</td>
<td>0.1662</td>
<td>0.0359</td>
<td>0.8498</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.1512</td>
<td>0.1913</td>
<td>0.6246</td>
<td>0.4293</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>0.2330</td>
<td>0.1870</td>
<td>1.5526</td>
<td>0.2128</td>
</tr>
</tbody>
</table>
The only significant parameters were SHS, age, and severe angina. Further examination of the effect of age on the model showed it to be non-linear, and the best model was obtained by using the dichotomous age parameter \( \leq 55 \) years. The final model presented in the manuscript also had the angina parameter changed to Class I/II so that all odds ratios were greater than one, which is more easily understandable.

12. Page 8 1st para. Were diabetes, prior CABG, and HF included in the model? The last paragraph of the background indicates that they have been found to be predictors of extent of EECP benefit.
Response: See above.

13. Page 9 "analysese" should be "analyses"
Response: Corrected.

14. The definition of SHS requires that the subject be living with another person. This presents some potential limitations which perhaps should be commented on in the paper. Subjects who live alone are clearly not exposed to SHS in their household, nor are they exposed to any other bad habits of a cohabitor. If smokers are more prone to, for example, poor diet or lack of exercise, then those living with them may have pressure to live similarly (re the NEJM "obesity is contagious" article). Hence it cannot be discerned whether the lack of EECP benefit is due to second-hand smoke, or just "second-hand lifestyle".
Response: This point is well-taken. We have added these comments to the Limitations section of the Discussion on pages 9-10.

All authors have approved this revision. Thank you for your careful consideration of this revised manuscript to *BMC Cardiovascular Disorders*.

Sincerely,

Andrew D. Michaels, MD, MAS, FACC, FAHA (on behalf of all co-authors)
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Associate Professor of Medicine, University of Utah