Author's response to reviews

**Title:** Pulmonary venous occlusion and death in pulmonary arterial hypertension: survival analyses using radiographic surrogates

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**Version:** 2 **Date:** 11 February 2011

**Author's response to reviews:** see over
Dear Prof. Dr. Shipley,

Thank you very much for giving us to revise our manuscript. Here we upload a new version of our manuscript. Generally speaking, we revised our paper extensively.

Firstly, we corrected the wording because both reviewers indicated the difficulty in understanding of the conclusions. Considering their comment, we are afraid that there is some trouble in our language. In our original version, we used the word “pulmonary venous occlusion” in both of the title and the text. This word naturally reminds readers pulmonary veno-occlusive disease (PVOD). However, as Reviewer #1 indicates, the radiographic signs do not directly surrogate development of PVOD but disturbance of pulmonary venous drainage, which may be observed in other types of PAH including CTD-associated PAH. We consider that the differentiation of the clinical entities between PAH and PVOD is now challenged. The relationship between PAH and PVOD has been discussed for a long time. PVOD was class 2.4 in the WHO classification (Evian Classification, 1998), and was class 1.4 in the Revised WHO Classification (Venice Classification, 2004), but now is class 1’ in Dana Point Classification (2008). After the issue of Dana Point Classification, Dr. Dorfmüller’s group and Dr. Overbeek’s group separately reported that obstruction of the pulmonary veins develops in considerable proportion of patients with idiopathic or CTD-associated PAH (Ref 3 and 4). Both groups reported that majority of CTD-associated PAH (Class 1.4.1 of Dana Point Classification) accompanies obstruction of the pulmonary veins as observed in cases of PVOD. Moreover, 17% of Dr. Dorfmüller’s patients with idiopathic PAH and 37.5% of Dr. Overbeek’s patients with idiopathic PAH had obstruction in the pulmonary veins. We consider it is very important and suggestive that either of the two groups did not refer idiopathic obstruction of the pulmonary veins as PVOD but as idiopathic PAH. This demonstrates that the differentiation of clinical entities between PAH and PVOD is currently challenged. To make our stance on this question clear, we added a following sentence to section of Background: “These findings challenge relationship between clinical entity of PAH and that of pulmonary veno-occlusive disease (PVOD)”.

Moreover, we
replaced “pulmonary venous occlusion” with “obstruction of the pulmonary veins” or “pulmonary venous obstruction”.

Secondly, we deleted the comments on potential benefit of antifibrous agents in patients with obstruction of the pulmonary veins. The both reviewers recommend this.

We uploaded thee files: “Original text”, “Revised text”, and “Tracked changes”. Please refer the file “Tracked changes” for examine the changes that we made. In the response to Reviewer #1 and #2, we reported the location of each correction of the manuscript by the number of line in file “Tracked changes”.

Besides the revision following Reviewer #1 and #2, we corrected the affiliation 2 from “Nagoya City Rehabilitation Centre” to “Nagoya City Rehabilitation Center”. We also corrected some typographical errors. We are very sorry for these errors. We made it clear that all the study participants gave informed consent in the section of Methods as following the editorial instruction.

We thank you for your consideration of the manuscript and we look forward to your reply, which we hope will be positive.

Sincerely yours,
Yutaka Takeda, MD.
Response to Reviewer #1’s comments

The authors appreciate the kind and intellectual review of Reviewer #1. Let us respond to the comments. We uploaded three files: “Original text”, “Revised text”, and “Tracked changes”. Please refer the file “Tracked changes” for examine the changes we made. We reported the location of each correction by the number of line of “Tracked changes” in the following sections.

The Reviewer #1 discusses the report by Montani et al. (Ref. 7) and provides the questions on diagnostic accuracy of the surrogates and recommended pathological examination for diagnosis of pulmonary veno-occlusive disease (PVOD). We agree with Reviewer #1 on the importance to review the diagnostic accuracy of the surrogates. Please refer the table. The table showed the sensitivity, specificity, and positive likelihood ratio of each surrogate reported by Resten et al. (Ref. 15) and Montani et al. (Ref. 7).

<table>
<thead>
<tr>
<th></th>
<th>Montani</th>
<th>Resten</th>
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</thead>
<tbody>
<tr>
<td>Mediastinal Adenopathy</td>
<td>Sensitivity</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Positive likelihood ratio</td>
<td>8.45</td>
</tr>
<tr>
<td>Septal Lines</td>
<td>Sensitivity</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Positive likelihood ratio</td>
<td>4.23</td>
</tr>
<tr>
<td>Ground Glass Attenuation</td>
<td>Sensitivity</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Positive likelihood ratio</td>
<td>2.82</td>
</tr>
</tbody>
</table>

Viewing these reports, you find that the diagnostic accuracy of each surrogate in Montani’s report acceptably agrees with that in Resten’s. In comparison between these articles, the reported diagnostic accuracy is slightly more excellent in Resten’s results than in Montani’s. These minor inconsistencies are may be due to the difference in the methods of CT scanning. Dr. Resten and his colleagues obtained the CT images in a similar procedure with us; their slice thickness was 1.0 mm but ours was 0.75 mm. Nevertheless, Dr. Montani’s group did not report the details of CT scanning. Because of this,
following the conclusion by Dr. Resten’s group, we consider that radiographic surrogates are acceptable.

We know that Reviewer #1 agrees with us on that the procedure of lung biopsy is extremely hazardous. We understand that pathological proof is favourable in diagnosis of pulmonary venous obstruction. However, we feel that lung biopsy is available in minority of patients. Because of this, even if some study demonstrated that the information by lung biopsy provides useful information for patients’ management, it would be knowledge hard to use. We earnestly hope that Reviewer #1 agrees with us in the potential usefulness of the results of this study in setting of clinical practice.

In association with this point, we made following changes.
1. From line 292 to 295
2. Line 311

Reviewer #1 recommends the revision of the wording of the title and text to clarify that we used only radiographic surrogates but no pathological examination. We consider that these are very important instructions. However, honestly telling, we wonder how to change the title. It is because the title already says “using radiographic surrogates”. In text, description of surrogate use seems clear.

Reviewing our original manuscript, we found that term “pulmonary venous occlusion” might cause trouble. “Pulmonary venous occlusion” naturally reminds readers PVOD. However, as Reviewer #1 indicates, the radiographic signs do not directly surrogate development of PVOD but disturbance of pulmonary venous drainage, which may be observed in other types of PAH including CTD-associated PAH. We consider that the differentiation of the clinical entities between PAH and PVOD is now challenged. The relationship between PAH and PVOD has been discussed for a long time. PVOD was class 2.4 in the WHO classification (Evian Classification, 1998), and was class 1.4 in the Revised WHO Classification (Venice Classification, 2004), but now is class 1’ in Dana Point Classification (2008). After the issue of Dana Point Classification, Dr. Dorfmüller’s group and Dr. Overbeek’s group separately reported that obstruction of the pulmonary veins develops in considerable proportion of patients with idiopathic or CTD-associated PAH (Ref 3 and 4). Both groups reported that majority of CTD-associated PAH (Class 1.4.1 of Dana Point Classification) accompanies obstruction of the pulmonary veins as
observed in cases of PVOD. Moreover, 17% of Dr. Dorfmüller’s patients with idiopathic PAH and 37.5% of Dr. Overbeek’s patients with idiopathic PAH had obstruction in the pulmonary veins. We consider it is very important and suggestive that either of the two groups did not refer idiopathic obstruction of the pulmonary veins as PVOD but as idiopathic PAH. This demonstrates that the differentiation of clinical entities between PAH and PVOD is currently challenged. To make our stance on this question clear, we added a following sentence to section of Background: “These findings challenge relationship between clinical entity of PAH and that of pulmonary veno-occlusive disease (PVOD)”. Moreover, we replaced “pulmonary venous occlusion” with “obstruction of the pulmonary veins” or “pulmonary venous obstruction”.

In association with this point, we made following changes.

1. From “pulmonary venous occlusion” to “obstruction of the pulmonary veins” or “pulmonary venous obstruction”
   1. Line 1 (Title)
   2. Line 36
   3. Line 37
   4. Line 44
   5. Line 55
   6. Line 67
   7. Line 69
   8. Line 71
   9. Line 72
   10. Line 74
   11. Line 93
   12. Line 95
   13. Line 136
   14. Line 159
   15. Line 175
   16. Line 177
   17. Line 224
   18. Line 225
   19. Line 229
   20. Line 232
   21. Line 233
   22. Line 236
23. Line 237
24. Line 238
25. Line 239
26. Line 243
27. Line 245
28. Line 247
29. Line 250
30. Line 251
31. Line 262
32. Line 266
33. Line 284
34. Line 285
35. Line 288
36. Line 290
37. Line 296
38. Line 299
39. Line 300
40. Line 306
41. Line 315
42. Table 2 (Title)

2. Comment on the differentiation between PVOD and other types of PAH
   1. Line 68
   2. Line 241

Reviewer #1 questions the basis for we described that that antifibrotic drugs may benefit patients with CTD-associated PAH. We guess that the obstruction of the pulmonary veins is fibrous from the Ref 3 and 4. However, this is indirect consideration. Following the suggestion by Reviewer #1, we deleted the comments suggesting the effects of antifibrous agents from our revised manuscript.

   In association with this point, we made following changes.
   1. Line 56
   2. Line 315
Reviewer #1 requires the cause of PAH in the 15 death cases. We counted the death cases of each cause. We observed that the difference between causes in the frequency of death does not reach statistical significance. We added the result to the section of Results. We also revised the section of Discussion. We added comments to the paragraph of the study limitation. Moreover, we entirely revised the paragraph on the causal discussion of the prognostic disagreement between the causes of PAH. We hope that Reviewer #1 find these description acceptable.

In association with this point, we made following changes.
1. Line 150
2. From Line 252 to 281
3. Line 307

Reviewer #1 indicated an error of Table 2. We fixed it. The numbers of frequency of ground glass attenuation in patients with idiopathic and CTD-associated PAH were replaced each other.
We corrected Table 2.

Reviewer #1 questions whether we excluded patients with CTEPH. Because we actually excluded them, we added a description on it to the section of Methods. We added a sentence (Line 89).

Following instruction of Reviewer #1, we make clear that we used two-sided p-values. We added a comment (Line 140).

Reviewer #1 recommends us to make our Results section more focused. We revised this section.
1. From Line 145 to 154
2. From Line 160 to 162
3. Line 163
4. Line 165
5. Line 169
6. Line 179
7. Line 181
8. From Line 182 to 186
9. Line 188
Response to Reviewer #2’s comments

The authors appreciate the kind and intellectual review of Reviewer #2. Let us respond to the comments. We uploaded the files: “Original text”, “Revised text”, and “Tracked changes”. Please refer to the file “Tracked changes” for examine the changes we made. We reported the location of each correction by the number of line of “Tracked changes” in the following sections.

Reviewer #2 recommends us to make clear the timeline of CT scans and situation at our radiologist made up their reports. To clarify these, we added comments to section of Methods. Despite the radiologists were not restricted from the other clinical data, it hardly seems to cause any bias. It is because the radiologists was not informed the purpose of the study until the beginning of writing this manuscript.

In association with this point, we made following changes.
1. Line 102
2. Line 104
3. Line 119

Reviewer #2 indicated that there was some bias in the patients’ population. As commented in section of limitation, we accept only select patients, the majority of whom had experienced treatment failure at their referring hospitals. Therefore, the frequency in the radiographic surrogates might be biased as well. Although this bias hardly seems to make the study conclusion unacceptable, we clarified the description of this bias in the section of limitation.

1. From Line 307 to 311

Reviewer #2 asks a question whether the predictive power is independent of mortality predictors other than plasma BNP concentration. We also think that this is an important question. However, we are afraid that multivariate analyses do not seem to have enough statistical power because of the small sample size. Instead, we provide data on the relationships between each radiological surrogate and patients’ characteristics in Table 2. This table may help readers to examine relationship between each radiographic surrogate
and other risk factors. Moreover, we added a comment to the section of study limitation in Discussion.

1. From Line 309 to 311

Reviewer #2 indicated that patients with CTD-associated PAH but not any radiographic surrogate have survival expectancy as good as patients with idiopathic PAH but not any surrogate. It is very our conclusion. To the best of our knowledge, there has not been published survival data with grouping the patients with or without radiographic surrogate for obstruction of the pulmonary veins. Not only that, there is few published report of direct comparison in survival rate between patients with and without pulmonary venous obstruction that is proved by lung biopsy. Therefore, we believe that this report is very important.

Reviewer #2 recommends us to revise the conclusion. Following the recommendation, we deleted the comments suggesting the effects of antifibrous agents from our revised manuscript.

1. Line 56
2. From Line 316 to 319