Author's response to reviews

Title: Pulmonary artery enlargement in schistosomiasis associated pulmonary arterial hypertension

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Author’s response to reviews: see over
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To Dr Jean-Philippe Bouchara
Associate Editor, BMC Pulmonary Medicine

Ref: Manuscript
“Pulmonary artery enlargement in schistosomiasis associated pulmonary arterial hypertension”

Dear Prof.

We would like to thank you for the opportunity of reviewing our manuscript entitled “Pulmonary artery enlargement in schistosomiasis associated pulmonary arterial hypertension”. The manuscript has improved as a result of the input from the reviewers. We have addressed the issues brought up by the reviewers, and included a point by point response. We have submitted the revised “Marked Copy” of the manuscript.

Again, thank you for considering this manuscript for publication in your journal BMC Pulmonary Medicine.

Sincerely,

Rogerio Souza, MD, PhD
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Response to Reviewers

Reviewer 1

The manuscript “Pulmonary artery enlargement in Schistosomiasis associated pulmonary arterial hypertension” by Hoette, et al is of special interest. It provided an evidence of what previously suspected that Schistosomiasis induced pulmonary hypertension is more likely to induce pulmonary artery dilation.

We would like to thank the reviewer for his comments and suggestions

Major Compulsory Revisions

1. In the “abstract “ line 42 of the manuscript and line 172 of the manuscript in the “Conclusion” section, It is advisable to change the word, “are a characteristic feature “ to “ more likely” as the authors have not provided Specificity and Selectivity analysis to be able they to claim word characteristic.

We agree that we should better limit our conclusions accordingly. We changed the conclusions as requested by the reviewer.

2. In the “Result” section the authors are advised to 
   a. Add standard deviation the age group (line 93 of the manuscript).

We added the standard deviation as suggested by the reviewer

b. All haemodynamic data are repeated as it was mentioned in the table, so suggest removing that data from the results and referred to the table as it will be more readable. Also is in the table, please add cardiac output data, and remove the P value and change to “ns” in LPAD to be consistent with the result of the table

All changes were made according to the reviewer’s suggestion

3. Line 103 –line 106 of the manuscript is an important part of the paper and the authors are encouraged to provide data to the reader, (by say provided a graph of mPAP vs MPAD). This will help to provide visual evidence to the reader.

We have added the requested figure as suggested by the reviewer.

Thank you for pointing this out; we corrected the reference.

Minor Essential Revisions

5. In the introduction and discussion, I notices that the authors have not referred to an important observation from northern Brazil by Ferreira RCS et al in “Prevalence of pulmonary hypertension in patients with schistosomal liver fibrosis “Annals of Tropical Medicine & Parasitology, Vol. 103, No. 2, 129–143 (2009)” where they documented clearly and in some details pulmonary artery dilatation in Schistosomiasis induced pulmonary hypertension.

The study mentioned by the reviewer is a study of prevalence of pulmonary hypertension based on echocardiographic measurements in patients with schistosomal liver fibrosis. There are important caveats in the study that prevent any comparison with our study. First, although echocardiogram is the best non-invasive tool to screen for the presence of PH in higher risk populations, it lacks adequate specificity to make the appropriate diagnosis as already demonstrated in several studies, including in schistosomiasis. Furthermore, echo does not allow the distinction between pre and post capillary pulmonary hypertension; two entities that might have completely different pathophysiological mechanisms. Also, the study only documented enlarged pulmonary arteries in patients with echocardiographic PH against patients with normal PASP levels, reinforcing the common findings of PH in the CT; however, the point of our study was to demonstrate a more pronounced dilatation in Sch-PAH as compared with IPAH.

6. In the limitation of the study, the authors have still to accept that the causality of Schistosomiasis to the patients labelled as Sch-PAH are based on empirical criteria (mentioned in line 70-72 of the manuscript) set by the authors, and although there is no accepted standard in the international guidelines that are evidence-based.

We agree with reviewer that there are no evidence-based criteria for the diagnosis of Sch-PAH. The same is also true for COPD associated pulmonary hypertension or other forms of pulmonary arterial hypertension. Indeed, the criteria that has been used by our group just raises the chance of the disease to be associated to schistosomiasis but this does not mean that Sch-PAH could not exist in patients without
other chronic manifestations of schistosomiasis; the problem is how to prove this association in such case.

We have included this limitation as suggested by the reviewer.

7. The authors attributed longer duration of illness in Sch-PAH as one of the possible cause of the pulmonary artery dilatation, although this is a plausible explanation, it will be useful to provide data in the manuscript for the duration of disease in the Sch-PAH (being a retrospective study) and probably a survival of the IPAH and Such PHT group to enhance this argument. (Also line 127-128, and line 139-146 of the manuscript).

We agree with the reviewer that this would further strength the argument about the duration of the disease as the potential cause for this enlargement, as suggested by some of the references included in the manuscript. However, due to the retrospective nature of this study, we do not have reliable data from the charts reviewed to allow such analysis.

We have included this point as a limitation of the study.

8. Although the paragraph starts with line 147 of the manuscript regarding that inflammatory processes are accurate, it may be difficult to argue that it can be applied to the causation of pulmonary dilatation. The real difference of the inflammatory process has not yet fully characterized between IPAH and Sch-PAH to help to attribute the difference in causation. Furthermore, the endothelial system signalling of the main pulmonary arteries are different from that small vessel where the remodelling took place. Suggestion: remove this paragraph (line 147-162).

Although we agree with the reviewer that there is still a lot to be demonstrated in terms of the role of inflammation not only in Sch-PAH but in all forms of PAH, we consider that this could be a plausible hypothesis. The point of including this within the discussion is exactly to raise the question about how much the profile of inflammation could influence the course of the disease in its various aspects, from the radiological presentation to even survival. Furthermore, although the remodelling process in PAH is predominant within the small arteries, this influences the capacitance of the whole arterial compartment, thus potentially influencing the stretching forces acting within the wall also of the main pulmonary arteries. Nevertheless, the presence of a specific adaptive vascular change or the influence of other pathophysiological mechanisms leading to pulmonary artery dilation and also to better long term survival can not be ruled out. In patients with abdominal aorta aneurysm (AAA), intrinsic properties of the artery wall have been suggested to explain aneurysm growth. Destruction of structural
connective tissue and inflammation are typical findings in aortic aneurysm, these findings suggest that inflammation in the arterial wall may play an import role in the dilation process.
Hoette and colleagues have investigated the presence of pulmonary artery enlargement in schistosomiasis-associated pulmonary arterial hypertension (Sc-PAH) in this retrospective study. This novel analysis adds key data to this unfortunately very prevalent but relatively understudied disease. They have observed that, relative to patients with idiopathic disease, Sc-PAH patients on average have significantly enlarged pulmonary arteries.

We would like to thank the reviewer for his comments and suggestions.

Major Compulsory Revisions:

1. Please plot the individual pulmonary artery measurements in a new figure, such as in the form of a vertical point plot with means and standard deviations indicated, to convey if the data are normally or non-normally distributed. In several places the authors use the term “aneurismal” which possibly implies a subset of patients with extreme dilation—perhaps the data instead show on average an increase in diameter.

Before any analysis was performed, distribution was tested with a kolmogorov-smirnov test in both samples, allowing the appropriate use of Student t test. In both groups we can find patients with extreme dilatation of main pulmonary artery (over 8 cm of diameter). Even excluding those cases, the results are maintained. We show below the requested plot although we are not sure about how much it will add to the manuscript. In this sense, we defer to the editor the decision about including it in the manuscript.
Minor Essential Revisions

1. Can the authors comment on how many Sc-PAH versus IPAH patients were treated with vasodilators at the time the CT scan was done? A prior publication by the same group (dos Santos Fernandes CJ et al. Survival in schistosomiasis-associated pulmonary arterial hypertension. J Am Coll Cardiol. 2010 Aug 24;56(9):715-20.) commented that at time, IPAH but not Sc-PAH patients were treated with vasodilator medications (methods section). This difference in treatment could also affect the pulmonary artery enlargement observed.

   We thank the reviewer for pointing this out. All data was collected as part of the baseline evaluation so that none of the patients was on specific therapy.

   We added this information within the methods section.

2. Line 4 of the abstract “whether or not this is a feature of Sch-PAH or a casual finding.” is unclear. I think the authors mean to say either (a) the prevalence of PA enlargement in Sc-PAH is greater than IPAH, or (b) on average the pulmonary artery is more enlarged in Sc-PAH than IPAH. Would rephrase.

   We have changed the text according to the reviewer’s suggestion.

Discretionary Revisions

1. In the discussion, the authors mention that a key factor may be chronicity of disease, i.e. Sc-PAH is more mild so may be more longstanding. Although I realize this may not be possible with the data available, if the data are available it would be helpful to know the duration between onset of symptoms in the Sc-PAH patients versus IPAH patients—it may be that in Sc-PAH the disease is more longstanding but hemodynamically more mild compared to IPAH.

   As we mentioned in the response to reviewer 1, these data would further strength the argument about the duration of the disease as the potential cause for the pulmonary artery enlargement, as suggested by
some of the references included in the manuscript. However, due to the retrospective nature of this study, we do not have reliable data from the charts reviewed to allow such analysis.

We have included this information as part of our study limitations