Reviewer's report

Title: Exhaled and arterial levels of Endothelin-1 are increased and correlate to pulmonary systolic pressure in COPD with pulmonary hypertension. An imbalanced output in the breath between Endothelin-1 and Nitric Oxide.

Version: 2 Date: 25 April 2008

Reviewer: Fanny WS Ko

Reviewer's report:

Comment:

This is an interesting paper that assessed the blood and exhaled breath condensate endothelin-1 (ET-1) and exhaled nitric oxide (FeNO) level in COPD subjects with and without pulmonary hypertension (PAH). It was found that COPD patients with PAH had higher blood and exhaled breath condensate levels of ET-1 and decreased exhaled FeNO level. This study adds some knowledge to the non-invasive assessment of biomarkers for patients with COPD with and without PAH.

Below are some of my concerns/queries about this study:

Major Compulsory Revisions

1. Ex-smoking COPD patients were recruited as controls for this study. How do you define ex-smokers (stopped smoking for 1 year?). Did you confirm the ex-smoking status of the subjects, e.g. by urine cotinine assay. If not, perhaps we should add this as a limitation of the study in the discussion.

2. Non-smokers were recruited as control for this study. Perhaps, ex-smokers with similar pack-years but with no airflow obstruction were better controls. This can be added as a limitation of the study in the discussion too.

3. How was atopy defined --- ? skin test, specific IgE level.

4. Group 3 had 4 subjects only and these subjects were patients with primary PAH treated with bosentan for at least 3 months. It is unsure whether it is meaningful to compare the COPD subjects with and without PAH with just 4 primary PAH subjects. How the treatment of bosentan for PAH has modified the measured parameters (ET-1 and FeNO) is also unknown. I suggest to remove this group of subjects in the paper.

5. On page 7, method section, paragraph 2, last 2 lines: it was mentioned that “reproducibility of repeated ET-1 measurements was assessed by the Bland and Altman method and the coefficient of variations”. I could not find the reproducibility data in the paper. How many subjects and what subjects had you recruited for the reproducibility assessment? Kindly present the reproducibility data.

6. In the results section: I found the presentation a bit confusing. In fact, on page
10-11, under the subtitle of “Group of COPD (Group 2)”, all the data presented in this paragraph (apart from the last 3 lines), had been presented in the paragraphs on page 9-10 under the subtitle “Group of COPD with PAH (Group 1). I would suggest to present the results under the subtitle of “ET-1” and “FeNO” instead and avoid repeating the already presented data.

7. I suggest the authors to add a paragraph on the limitations for this study. Some points have been already mentioned in my comments above (like points 1 and 2).

Minor Essential Revisions
1. On page 9, last 2 lines: “Overexpression of ET-1 was found in COPD with PAH compared to COPD only”. I think it should be “…..compared to both the COPD patients without PAH and healthy controls”.
2. Page 10, first line: “linear regression analysis showed a good correlation….” Should it be Pearson correlation analysis rather than linear regression analysis?

Discretionary Revisions
1. It would be of interest to see if ET-1 levels in plasma and exhaled breath condensate correlated with FEV1 and PaPs in all the COPD subjects (i.e. Group 1 + Group 2 subjects).
2. When reading Figure 1-3 and 8, the first column was COPD without PAH (Group 2), followed by COPD+PAH (Group 1), followed by IPAH (Group 3) and finally HS (Group 4). I think it is easier for the reader if the position of the data can be grouped from the right to left in the order of Group 1, Group 2, Group 3 and then Group 4. It is a bit confusing when referring to the “Groups” when the graphical presentation is not in numerical order.
3. Page 9, second paragraph, line 2: consider deleting “FEV1%39.35±11.45, FEV1/FVC% 46.95±6.81, PaPs#35mmHg” as these data were already presented in Table 1. Similar issue on page 10, paragraph 3, line 1.
4. The discussion section can be divided into smaller paragraphs for more easy comprehension. Example: Can consider next paragraph on line 10 of the discussion “Our findings show…..”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.