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: 30 April 2008

Reviewer: Deborah Yates

Reviewer's report:

This is an interesting paper which covers an important area. It has been clearly written and carefully presented. The results are highly significant (contrasting with other work available in abstract form on this topic and previous publications on FENO in COPD. Despite the authors' clear conclusions, it is important that all other potential explanations for the results are considered.

Major compulsory revisions.

1. Title: This should be cut and stopped after "hypertension." The rest of the title is speculative. The same is true for line 15 of the abstract, which should be deleted. The paper is observational and cannot be used to deduce mechanisms.

2. Methods:
   A. Subjects: Further details are needed regarding the medications taken by the patients as these are likely to have had a significant effect on FENO, and possibly also EBC. Oxygen therapy and steroids in particular, inhaled or otherwise, should be documented as well as other medications e.g. antihypertensives, glyceryl trinitrate etc as these are known to affect FENO. Were patients studied when clinically stable and at least 6 weeks after a respiratory tract infection? It is well known that this affects FENO. Also, information about atopy in COPD and other patients should be documented as FENO is increased in atopics. The groups are imbalanced with regard to gender and numbers and the IPAH group is too small for meaningful comparison.
   B. Echocardiography is known to be difficult and insensitive in COPD and although the technique is adequate it is probably unwise to use it as the gold standard for diagnosing and pulmonary hypertension and assessing its severity. Do the authors have any data on right heart catheterisation (which presumably would have been done in some patients)? If so, it should be added.
   C. Statistics. As EBC ET-1 is relatively new, an assessment should be made of its distribution (normal or otherwise) before applying statistical tests. If this is not normally distributed, it is not appropriate to apply a t-test but a non-parametric test should be used. Also, the reproducibility of the assay should be reported and a power calculation presented. The study is very likely to be underpowered, particularly as the numbers in some groups (e.g. IPAH) is very low.

Results:
A. Table 1 does not agree with the results in the text. The last sentence specifies that there were no significant differences between groups for all parameters other than PaPs, which cannot be true as the smoking history, age, gender and lung function are very different. The authors have not mentioned these but they may well affect both EBC ET-1 and FENO. (See Taylor, Olin, Travers on FENO reference values). Also, did they classify COPD by severity?

B. Although the 6 minute walk and echo results are mentioned in the methods there is no reference to these and to their correlation with results. It is a pity that the COPD alone group did not have their 6 minute walks reported (if done) as they differ from the COPD/PH group in FEV1 (i.e. less severe) and if the 6 MWT had been similar this would have strengthened the argument that the differences between these groups is not due to differences in severity.

C. Unfortunately, insufficient information has been given and the numbers are too small to be sure that the good correlations observed are not due to differences between the groups.

Discussion

A. The discussion does not cover any other potential reasons for the study results (e.g. confounding by drug effects, severity, small numbers, sex imbalance) nor cite all the most recent literature (some of which is currently available in abstract form e.g. Warwick, ATS 2007 and which has recently been published e.g. Lankeit, AJRCCM May 2008). As mentioned earlier, discussion of mechanisms is outside the scope of the paper.

Minor essential revisions

A. While accepting that the paper is carefully and overall clearly written, it is clear that English is not the authors’ mother tongue. It would be significantly improved (particularly the abstract, introduction and discussion) if many minor corrections were made by a native English speaker. This is not to complain, but would clarify the authors’ intentions (e.g. line 11 of the discussion, where "all" patients with COPD are said to have increased ET-1).

Discretionary revisions

A. Is Fig 9 really necessary?

C. The grant support has not been listed.

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I have no financial competing interests but I feel bound to declare that I have recently submitted two other papers which cover the same area (a review (now accepted) and a paper on a very similar topic (under review)).