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: 16 April 2008

Reviewer: Konstantinos Kostikas

Reviewer’s report:

The present study by Carraro and co-workers has evaluated the levels of endothelin-1 in arterial and venous blood and in exhaled breath condensate (EBC) of patients with COPD with and without pulmonary hypertension. They have shown that endothelin-1 is detectable in all samples and that its levels are elevated in patients with COPD, especially in the presence of pulmonary arterial hypertension (PAH). In addition, they have shown that patients with COPD and pulmonary hypertension present lower exhaled NO levels compared to patients with COPD alone, therefore presenting an imbalanced output of endothelin and NO in the exhaled air of patients with COPD and pulmonary hypertension. The concept of the study is rather novel and they present some interesting findings. However, there are several methodological issues that need to be addressed by the authors.

Major Comments

1. The inclusion of 4 patients with idiopathic pulmonary arterial hypertension does not add much to the concept of the study, especially since those patients are already treated with an endothelin-receptor antagonist (bosentan). My opinion is that those patients should not be included in the analysis.

2. Controls were non-smokers. A better option for controls would have been ex-smokers with similar smoking habit without COPD. Smoking is a significant confounder in exhaled NO measurements and may be involved in EBC measurements too. How long had the COPD subjects quit smoking?

3. Did the investigators measure DLCO during pulmonary function testing? If so the DLCO values should be reported, since they represent a significant measure in the evaluation in both the patients with COPD and those with PAH.

4. Doppler echocardiography was used to assess pulmonary arterial pressure. However, the gold standard remains a right heart catheterization, especially for research purposes. The authors should comment on their choice and they should refer to this as a major limitation of the present study.

5. Why was 6-minute walking test performed in only a subgroup of patients?

6. Exhaled NO levels are impressively high in some COPD patients. How did the authors exclude the presence of asthma in their subjects?

7. The statistical analysis is obviously based on the hypothesis that the data
present normal distribution. Did the authors use a specific test to check for normality of distribution of data (e.g. Shapiro-Wilks or Kolmogorov-Smirnoff?) If not, they should do so and use appropriate tests in the case of skewed data.

Minor Comments:
The article needs to be reviewed by a native English speaker.

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 declare that I have no competing interests