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CORRESPONDENCE

Circulating endothelin-1 and obstructive sleep apnoea

To the Editor:

We read with great interest the article by GRIMPEN *et al.* [1] entitled "Endothelin-1 plasma levels are not elevated in patients with obstructive sleep apnoea". Although we appreciate the hard work done, we feel that the authors have extended their conclusions beyond the study undertaken.

Elevated plasma endothelin-1 (ET-1) 1evels are a nonspecific marker of endothelial dysfunction due to cardiovascular, renal or pulmonary disease. As far as we are aware, there is no dose/response relationship depending on the number of pathological conditions that have caused the endothelial dysfunction. Neither is there reason to assume that a patient with hypertension, coronary artery disease (CAD) and obstructive sleep apnoea (OSA) will have a higher ET-1 1evel than a control with only hypertension and CAD. The problem cannot be resolved by matching control subjects with hypertension or CAD.

The study of PHILLIPS *et al.* [2] (January 1999), reporting a significant increase in ET-1 levels after 4 h of untreated severe OSA and a decrease after 5 h of nasal continuous positive airway pressure, was not cited. While discussing our preliminary report [3], GRIMPEN *et al.* [1] did not mention important differences in patient groups: our patients had more severe OSA and a higher body mass index. They were also 12 yrs younger, nonsmokers not receiving medication and had no chronic diseases other than OSA (and hypertension in the hypertensive group), whereas the majority of the patients and controls in the study of GRIMPEN *et al.* [1] received medication for cardiovascular diseases.

It would be interesting to know the smoking history of the patients and controls. Smoking causes endothelial dysfunction even in the absence of hypertension or CAD [4]. Elevated ET-1 levels have been reported in chronic obstructive pulmonary disease without coexisting pulmonary hypertension [5]. As the authors stated, mild pulmonary hypertension is often seen in patients with OSA. We are not aware of reports comparing ET-1 levels in venous and arterial blood in patients with this type of secondary pulmonary hypertension.

In future studies, it may be useful to focus on younger age groups in earlier stages of obstructive sleep apnoea and "endothelial dysfunction. Before stating that endothelin-1 plasma levels are not elevated in patients with obstructive sleep apnoea", arterial endothelin-1 levels should be measured in conjunction with apnoeas in patients without other sustained cardiovascular diseases.

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From the authors:

We greatly value S. Saarelainen's and J. Hasan's interest in our study [1]. It was pointed out that there have not been any studies showing a dose response relationship between the number of pathological factors and endothelin (ET)-1 plasma levels. As far as we are aware, however, such a relationship has never been denied either. We feel that this is an issue that has to be further investigated. It is well known that ET-1 production is triggered in cardiovascular diseases. Therefore, a finding of increased ET-1 plasma levels in patients with obstructive sleep apnoea (OSA), who have a distinctly higher incidence of cardiovascular diseases, could not prove that obstructive apnoeas are an independent cause of elevated ET-1 levels if compared to healthy controls. This is why the method of matching the controls for age, sex, presence of coronary artery disease (CAD), and arterial hypertension seems imperative to us.

We very much appreciate the study by PHILLIPS *et al.* [2] which reports an increase in ET-1 levels after 4 h of untreated sleep in OSA patients. It is likely that the discrepancy in results is due to the differences in patient characteristics. The authors studied patients with an average body mass index (BMI) of 42 and an average apnoea/hypopnoea index AHI of 74, while our patients only had an average BMI of 30 and an AHI of 41. It is obvious that patients with more severe OSA as studied by PHILLIPS et al. [2] and SAARELAINEN *et al.* [3] undergo more severe oxygen desaturations as a trigger of ET-1 secretion.

It is commonly accepted that smoking impairs endothelial function. However, former studies have shown that smoking has only a short-term effect on ET-1 plasma levels, if any [4]. Furthermore, only 5 of our 29 patients were smokers. Their plasma levels of ET-1 were not significantly different from the nonsmokers' (43.5 *versus* 41.25 $pg \cdot mL^{-1}$, p=0.7), neither was the average AHI (52 *versus* 39, p=0.3).

We agree that a study on young patients with severe obstructive sleep apnoea but without arterial hypertension or other cardiovascular diseases compared to matched controls would be ideal to further elucidate the role of endothelin-1 in obstructive sleep apnoea.

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