

# ET-1 and Cardiovascular Events in Obstructive Sleep Apnoea Patients

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## Background

Obstructive sleep apnoea (OSA) is a major public health issue, in part because of its cardiovascular consequences. OSA is an independent risk factor for systemic hypertension, coronary artery disease and stroke<sup>1</sup>. Intermittent hypoxia resulting from repetitive apnoeas induces endothelial dysfunction, inflammation and atherosclerosis and thus appears to be the main causal factor in the pathogenesis of cardiovascular morbidity<sup>1</sup>.

Markers of the cardiovascular risk associated with OSA could help identify at-risk patients and optimise treatment strategy. In OSA patients, some clinical studies have demonstrated increased plasma concentrations of endothelin-1 (ET-1)<sup>2-7</sup>, correlated with the severity of nocturnal hypoxia<sup>2</sup> and were corrected by treatment<sup>2,4</sup>. However, other studies failed to demonstrate such an increase<sup>8-11</sup>.

We hypothesised that OSA patients with a recent history of cardiovascular event would have higher plasma ET-1 levels, not only than matched OSA patients with no such history, but also than matched non-OSA patients with a similar cardiovascular history.

## Patients

Since 2000, a serum bank has been established from approximately 150 OSA patients included in several clinical research protocols from our laboratory. All patients underwent overnight polysomnography (PSG) to confirm the diagnosis of OSA, defined by a respiratory disturbance index (RDI)  $\geq 15$ /hour. Healthy normal volunteers were also included after an overnight PSG to confirm the absence of OSA.

In all patients and normal subjects, morning blood samples were collected and stored for future studies on biomarkers. In addition to PSG parameters, the following data were recorded: age, sex, body mass index (BMI), smoking and medical history with emphasis on a recent cardiovascular event (CVE - stroke or acute coronary syndrome), current pharmacological treatment, 24 hour monitoring of arterial blood pressure (BP) and carotid intima-media thickness (IMT). Among these individuals, four groups of subjects were matched for age, sex and BMI: OSA patients with a recent CVE (OSA-CVE group); patients without OSA but recent CVE (CVE group); OSA patients with no history of CVE (OSA group); and a control group of healthy subjects (C group) (Table 1).

**Table 1.** Main characteristics of the four subject groups

	OSA-CVE n=20 (1 female)	CVE n=12 (2 females)	OSA n=32 (6 females)	C n=16 (6 females)
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Age (years)	53.8 ± 8.8	52.5 ± 9.1	51.2 ± 8.9	45.8 ± 7.9
BMI (kg/m <sup>2</sup> )	25.7 ± 3.5	24.8 ± 2.7	25.6 ± 2.7	23.9 ± 3.3
RDI (per hour)	38.1 ± 18.1	9.4 ± 4.2	42.1 ± 16.2	7.4 ± 4.4
T90 (%TST)	5.19 ± 13.5	1 ± 2.5	3.7 ± 6.4	0.04 ± 0.1

Data are presented as mean ± SD. Age and BMI were not different in the four groups. BMI and T90 were not significantly different between the two OSA groups and between CVE and control subjects. BMI and T90 were significantly different ( $p < 0.05$ ) between the two OSA groups and CVE and between the two OSA groups and control subjects.

## Methods

### Measurements

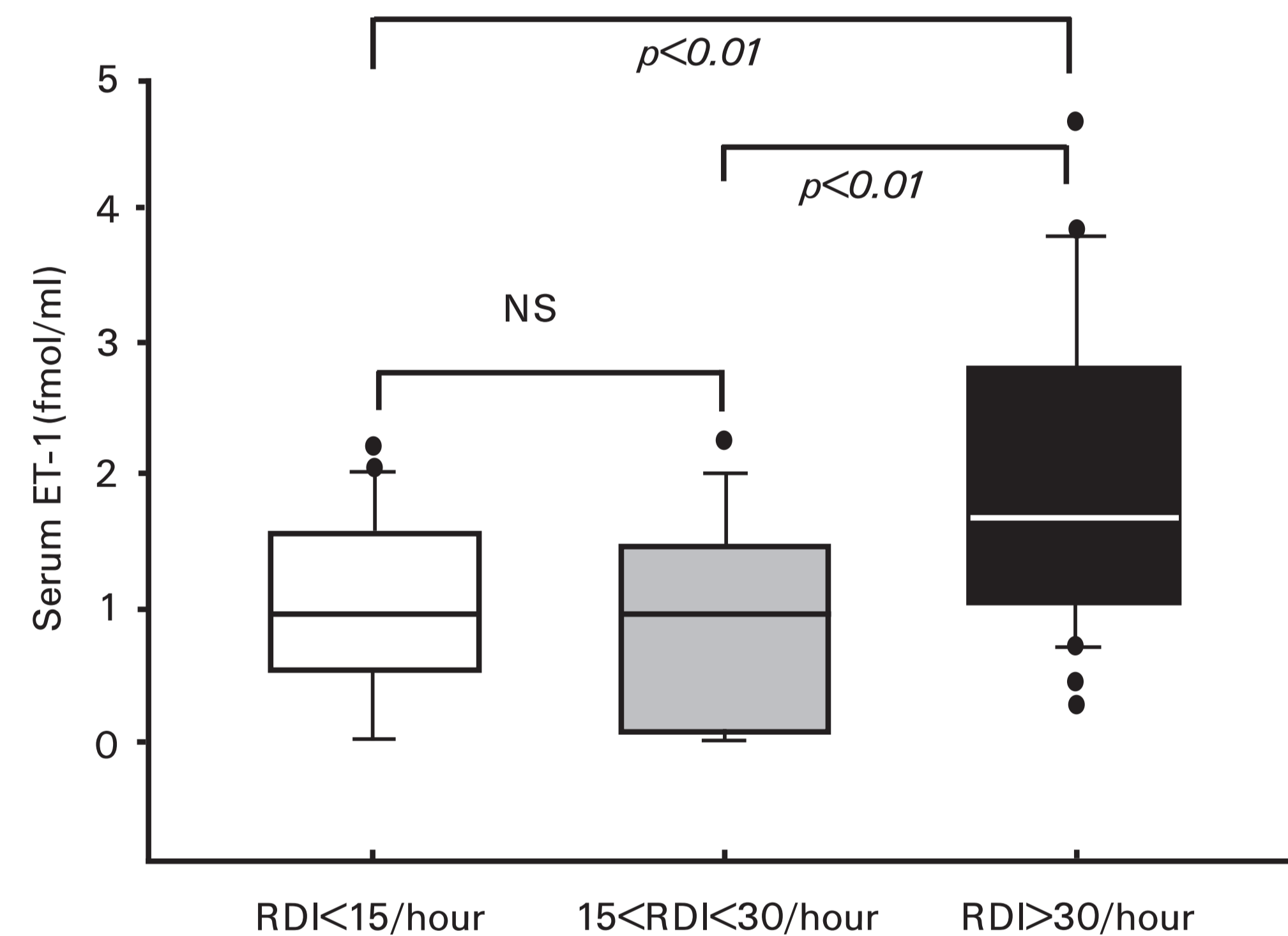
- PSG parameters: RDI, mean and minimal oxygen saturation, percentage of total sleep time (TST) spent at an oxygen saturation below 90% (T90). Levels of OSA severity were mild to moderate if  $15 < \text{RDI} < 30$ /hour and severe if  $\text{RDI} > 30$ /hour
- Serum ET-1 levels (ELISA, in duplicate)
- Arterial BP: mean daytime and nocturnal systolic and diastolic BP
- Carotid mean and maximum IMT

### Data analysis

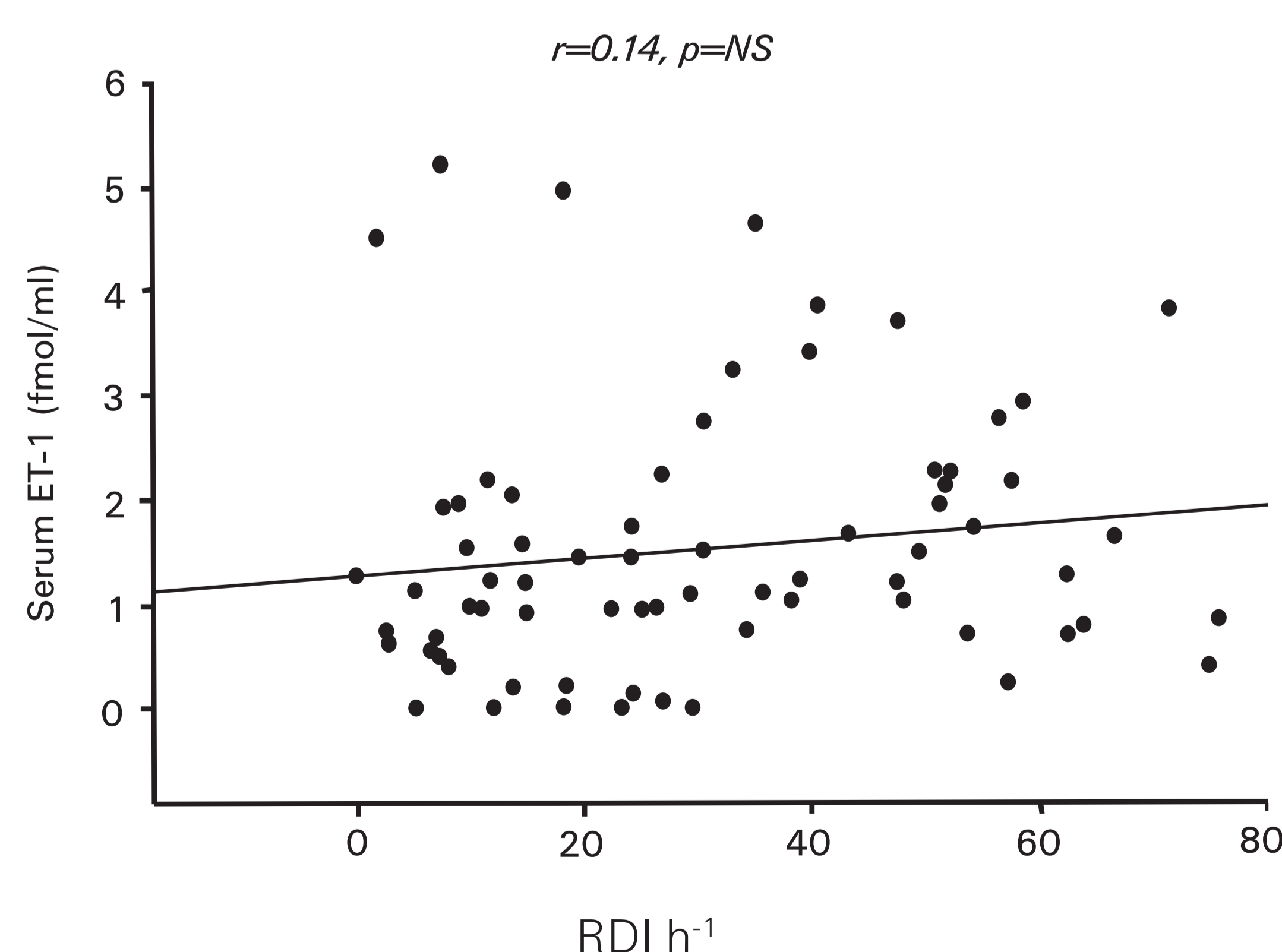
Normality of distribution was tested using Kurtosis and skewness tests. As most variables of interest were not normally distributed, statistical comparisons were performed with non-parametric tests.

Statistical significance was achieved for  $p$  values  $< 0.05$ .

**Figure 1.** ET-1 concentration in subjects grouped according to the severity of OSA



**Figure 2.** Relationship between ET-1 concentration and OSA severity

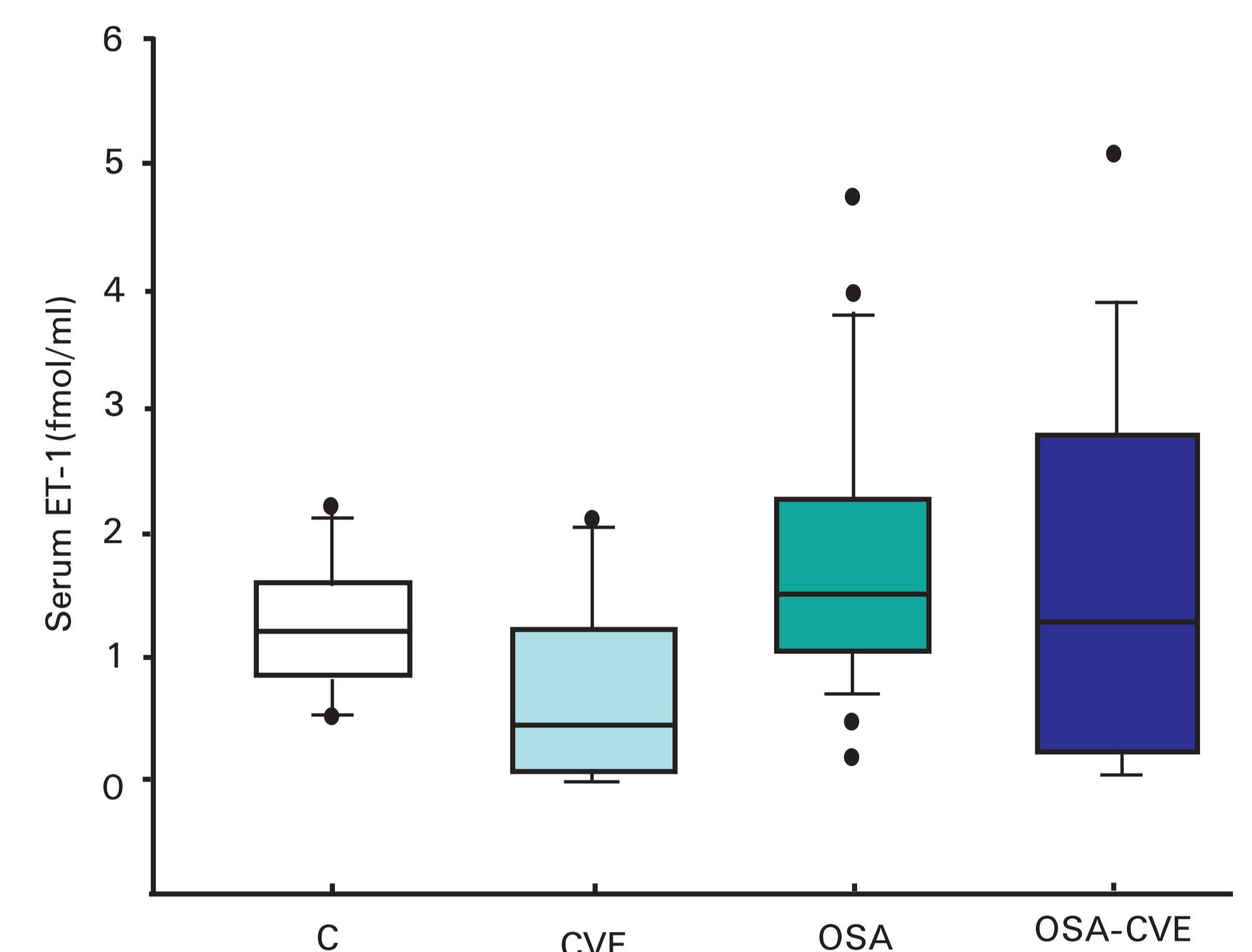


Pooled values from the four groups,  $n = 84$

## Results

- Regardless of their CVE status, severe OSA patients had significantly increased circulating ET-1 levels compared with moderate OSA patients or normal subjects (Figure 1).
- No correlation was found between serum ET-1 concentrations and the RDI (Figure 2) or the desaturation severity index T90 nor with diurnal/nocturnal blood pressure levels and carotid IMT.
- Circulating ET-1 levels were not significantly different between OSA patients with or without CVE. Overall, OSA patients had significantly higher ET-1 concentrations than their respective controls (Figure 3).

**Figure 3.** Serum ET-1 concentrations in the four subject groups



Comparison between groups was not statistically significant.

## Conclusions

The results of this study suggest that, contrary to our hypothesis, circulating ET-1 levels are not predictive of the cardiovascular risk in patients with OSA.

However, our study confirms that OSA patients have higher ET-1 levels than controls, underlining the need for further investigations of the ET-1 system in OSA-associated cardiovascular disease.

## References

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