Treatment for obstructive sleep apnoea: effect on peripheral nerve function

Rainer Dziewas, Matthias Schilling, Philipp Engel, Matthias Boentert, Hyon Hor, Angelika Okegwo, Peter Lüdemann, E Bernd Ringelstein, Peter Young

Background and objective: Obstructive sleep apnoea (OSA) is suggested to be associated with peripheral nerve damage. A case-control study was conducted to provide further support to this observation. In a longitudinal intervention study, it was examined whether treatment for OSA has a possible beneficial effect on peripheral nerve function.

Methods: Participants were 23 patients with OSA and 23 controls matched for age and body mass index (BMI), all without any known cause of peripheral nerve damage. The sensory nerve action potential (SNAP) amplitudes of both sural nerves were determined. After 6 months of treatment for OSA, treatment compliance was evaluated and nerve conduction studies were repeated.

Results: Patients with OSA had significantly lower mean (standard deviation) sural SNAP amplitudes than controls (6.3 (3.5) v 11.2 (5.0), p = 0.001). Multivariate regression analysis including the variables age, BMI and Apnoea–Hypopnea Index (AHI) showed that both age (p = 0.01) and AHI (p = 0.05) were inversely related to the SNAP amplitude. On follow-up, the sural SNAP showed an increase of 2.6 mV on average (p = 0.001). Multivariate regression analysis including the variables age, BMI, AHI, pretreatment SNAP and treatment compliance identified only treatment compliance as being significantly related to the SNAP increase (p < 0.005).

Conclusion: OSA is an independent risk factor for axonal dysfunction of peripheral sensory nerves. Impaired neural function is at least partly reversible with treatment for sleep apnoea.

Obstructive sleep apnoea (OSA) is a common disorder with an estimated prevalence in the general population of 2–5%. Its main clinical features are loud snoring and breathing stoppage during sleep. Owing to non-restful sleep, patients with OSA experience excessive daytime sleepiness and related neuropsychological impairments. By different pathophysiological mechanisms, OSA is known to be associated with arterial hypertension, a hypercoagulable state, decreased cerebral perfusion, arteriosclerosis and severe cardiac arrhythmias, all of which potentially contribute to the increased mortality and cerebrocardiovascular morbidity of patients with OSA.

Apart from that, an association of OSA with damage to the peripheral nervous system has been described only recently. Thus, we reported an increased prevalence of axonal sensory polyneuropathy in patients with OSA. This study found a decreased sural sensory nerve action potential (SNAP) in patients with OSA compared with controls. Additionally, a correlation of axonal dysfunction with the extent of oxygen desaturation was observed. We hypothesised that intermittent hypoxaemia is an independent risk factor for axonal dysfunction of peripheral nerves.

This study had two aims: (1) to replicate our previous results in another case-control study, thereby providing further support to the assumed pathophysiology; and (2) to examine a possible, beneficial effect of treatment for OSA on peripheral nerve function in a longitudinal intervention study.

Patients and methods

Patients
We included 23 patients with newly diagnosed OSA in the study. In each case, OSA was diagnosed by polysomnography (overnight recording of sleep–wake cycles, electrocardiogram, electroencephalogram, electromyogram, anterior tibialis electromyogram, oronasal air flow, chest wall and abdominal wall effort, and pulse oximetry). All individuals with OSA had an Apnoea–Hypopnea Index (AHI) of >10. Apart from the AHI, the percentage of night time with oxygen saturation below 90% (CT90) was determined.

Controls
Controls (n = 23) were admitted to hospital for suspected OSA that was not confirmed by polysomnography (17 were diagnosed with uncomplicated snoring, 4 with periodic limb movements and 3 with poor sleep hygiene). All controls had AHI <5. Controls were matched for age and BMI to the patients with OSA.

Patients with OSA and controls with a known cause of polyneuropathy such as diabetes mellitus, alcoholism, renal failure, carcinoma, disorders of immune-mediated injury and use of neurotoxic drugs were excluded from the study. In all participants, levels of fasting glucose, haemoglobin A1c, creatinine and hepatic enzymes were within the normal laboratory range. No patient had baseline hypoxia.

Nerve conduction studies were performed on a Keypoint electromyographical system (Dantec, Skovlunde, Denmark) using standard techniques as described previously. Skin temperature was maintained at 34°C during measurement. The base to peak amplitude of SNAP of both sural nerves was averaged. The investigator was blinded to the result of the sleep study.

Abbreviations: AHI, Apnoea–Hypopnea Index; BMI, body mass index; CT90, percentage of night time with an oxygen saturation below 90%; nCPAP, nasal continuous airway pressure; OSA, obstructive sleep apnoea; RICF, resistance to ischaemic conduction failure; SNAP, sensory nerve action potential
studies showed a significant difference in the mean sural SNAP amplitudes between both groups, with patients with OSA having significantly lower amplitudes than controls (table 1).

Multivariate regression analysis taking into account all 46 participants and including the variables age, BMI and AHI showed that both age (p<0.01) and AHI (p<0.05) were inversely related to the SNAP amplitude (table 2A).

In all patients with OSA, treatment led to a normalisation of the AHI. With a relative usage of nearly 83% of all nights, treatment compliance was generally good. However, there was a high interindividual variation as shown by a range of 10–100%. Although 14 patients used the device more than 90% of all nights, 9 patients had a usage below 90% and 5 of these showed a poor compliance of below 70%.

Patients with OSA with good and moderate or bad compliance did not differ with regard to basic epidemiological and sleep parameters (table 3). Overall, on follow-up, the sural SNAP showed on average an increase of 2.6 μV, which was highly significant (table 3). This effect was mainly due to the SNAP increase found in the high-compliance group, whereas patients with a moderate or poor compliance showed only a minimal improvement in SNAP amplitudes. In line with univariate statistics, multivariate regression analysis including the variables age, BMI, AHI, pre-treatment SNAP and treatment compliance identified only treatment compliance as being significantly related to the SNAP increase (table 2B).

### DISCUSSION

With the first part of our study, we confirmed our previous results.11 Thus, in patients with OSA, the sural SNAP amplitude was nearly 5 μV less than that in controls, a difference that was also found in the previous investigation. Multivariate regression analysis including all participants further showed that the amplitude of the sural SNAP was inversely related to the AHI and to age. Therefore, apart from increasing age, which has long been known to be associated with peripheral nerve dysfunction,14 sleep apnoea may constitute an additional independent risk factor for predominantly axonal sensory nerve damage. As, in the same analysis, the BMI showed no correlation with the sural SNAP, the difference between patients with OSA and controls is not attributable to an increased subcutaneous fat in the OSA group. As a limitation to these findings, we have to admit that other conditions associated with peripheral nerve damage, such as peripheral vascular disease, impaired thyroid function and decreased

### Statistical analysis

For statistical analysis, STATISTICA for Windows version 4 was used. Univariate comparisons were carried out with the t test for paired and unpaired data, as appropriate. Multivariate regression analysis was performed to identify variables correlated with the pretreatment SNAP amplitude and to assess parameters associated with an increase in the SNAP amplitude on follow-up.

### RESULTS

Patients with OSA and controls were well matched for age. Patients were more obese than controls, although this difference did not reach significance. As expected, patients had on average a more than tenfold higher AHI than controls. A similar difference was found for CT×90. As expected, we found a highly significant correlation of AHI and CT×90 across all participants (Spearman’s R = 0.96, p<0.0001). Nerve conduction studies showed a significant difference in the mean sural SNAP amplitudes between both groups, with patients with OSA having significantly lower amplitudes than controls (table 1).

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levels of vitamin B₁₂ and folic acid, have not been systematically studied here and may therefore bias our results.

The second part of our study further corroborated the previous results by finding a considerable increase in the sural SNAP amplitude 6 months after initiation of OSA treatment. As shown by multivariate regression analysis, treatment compliance was the only variable significantly associated with improved neural function. We may therefore assume that neural dysfunction is at least partly reversible with treatment in patients with OSA. Interestingly, the extent of pre-existing nerve damage had no effect on the subsequent treatment effect, suggesting that despite exposure to intermittent hypoxaemia possibly lasting several years, pathophysiological changes are partly functional rather than structural.

To the best of our knowledge, only one study has examined the effect of nCPAP treatment on peripheral nerve function in a small collection of patients with OSA. Mayer et al.¹⁰ used the resistance to ischaemic conduction failure (RICF) as a neurophysiological marker of peripheral nerve dysfunction.¹⁰ RICF is characterised by abnormal persisting nerve conduction during ischaemia and is one of the earliest abnormalities of peripheral nerve function in various metabolic conditions such as diabetes, chronic hypoxia and chronic renal failure.¹⁵–¹⁷ The authors found RICF in 7 of 17 patients with OSA and in none of the controls. After 2 months of nCPAP treatment, four patients with OSA with RICF were re-evaluated. In all of them this neurophysiological abnormality had disappeared, whereas pre-ischaemic nerve conduction parameters were unchanged and suggested persisting axonal dysfunction.

CONCLUSION
Just like chronic hypoxaemia caused by chronic obstructive pulmonary disease,¹⁶–¹⁸ recurrent intermittent hypoxaemia may be an independent risk factor for peripheral sensory nerve dysfunction. Secondly, comparable to the effect observed in other OSA-related disorders such as hypertension,²⁰ thrombophilia²¹ and cardiac rhythm disturbances,⁷ treatment for OSA might also result in improved function of peripheral nerves.

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