EDITORIAL

CPAP treatment of sleep apnoea in the early phase of stroke: growing evidence of effectiveness

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Sleep apnoea has been shown to be a cardiovascular risk factor [1, 2], presumably with a major role attributable to intermittent hypoxia [3, 4]. Early reports have suggested a relationship between sleep-disordered breathing and stroke [5–8]. The association between sleep apnoea and both prevalent and incident stroke has been further established in general population cohorts [9, 10]. Specifically, the Wisconsin Sleep Cohort provided prospective evidence that sleep-disordered breathing precedes stroke and may contribute to the development of stroke [9]. The prospective analysis of the Sleep Heart and Health Study also showed, in males <70 yrs of age, a strong adjusted association between ischaemic stroke and apnoea-hypopnoea index (AHI) in mild-to-moderate sleep apnoea [10]. In this subgroup of middle-aged males, in the mild-to-moderate range of severity (AHI 5–25 events·h⁻¹), each one-unit increase in AHI was estimated to increase stroke risk by 6%. It has also been shown that stroke and sleep apnoea are associated with increased mortality [8, 11]. However, in a recent meta-analysis of 2,343 ischaemic or haemorrhagic stroke and transient ischaemic attack (TIA) patients, obstructive sleep apnoea (OSA) was very common, irrespective of the type of stroke or timing after stroke [12]. Regardless of whether the studies were performed in acute stroke units or rehabilitation units, OSA was found in >50% of the stroke patients. Also, central events were limited to 7% of the total number of abnormal respiratory events during sleep. Consequently, as this association between sleep apnoea and stroke has been demonstrated, treating sleep-disordered breathing could be expected to be beneficial [13, 14]. The role of continuous positive airway pressure (CPAP) in stroke patients presenting with sleep apnoea is, however, still under discussion. It remains uncertain whether CPAP is feasible in these patients with a long-term acceptance that seems much lower than in other patient subgroups and requires caution with respect to haemodynamic tolerance [14–17]. Also, whether CPAP is able to significantly alter stroke outcomes remains to be established. Although there are positive data from recent studies [18, 19], there are also conflicting data with limited benefit and possible deleterious effects [20].

In this issue of the *European Respiratory Journal*, PARRA *et al.* [21] report on a randomised controlled trial (RCT) assessing the impact of CPAP in ischaemic stroke patients followed for 2 yrs. Stroke patients with an AHI ≥ 20 events·h⁻¹ were randomised either to early CPAP within the first 3–6 days after stroke or conventional treatment. CPAP led to an earlier improvement in neurological symptoms and a reduction in cardiovascular events, but there was no improvement in patients' survival or quality of life [21]. This is the first study of early CPAP carried out in a homogeneous group of patients with acute, first-ever ischaemic stroke. Potential beneficial effects of CPAP being administered earlier (*i.e.* within the first 24 h) with the stroke in progress cannot be excluded. It is also possible that the studied population was not fully representative of usual stroke patients. Severe stroke patients were likely to be excluded because only first-ever stroke patients with unaltered level of consciousness were eligible. The sample size of this study is also an issue. The study is probably slightly underpowered, which may explain why the cardiovascular event-free survival after 24 months was similar in both groups and also why the cardiovascular mortality rate, although being 0% in the CPAP group and 4.3% in the control group, was also not statistically different. Finally, the study was analysed in a per protocol and not an intention-to-treat manner, as the patients who did not tolerate CPAP were excluded from the analysis. Nevertheless, this remains the first study of this nature and, as such, is an important step forward.

Blood pressure control is a key issue in the acute management of stroke. There is evidence that CPAP may significantly reduce blood pressure [22, 23], although this is a limited reduction when compared with antihypertensive treatments (*e.g.* 2 versus 9 mmHg) [24]. Amazingly, a 2-mmHg decrement in blood pressure was recently obtained after only 1 yr of CPAP treatment (nonsignificant change at 3 and 6 months) in nonsleepy patients by the Spanish research network [25]. The evidence regarding CPAP impact on cardiovascular morbidity has been established by longitudinal studies [26]. By definition, patients were not randomised and the different subgroups studied may not be fully comparable. This is the reason why several RCTs are currently being conducted in the USA [27], Spain [25], Australia and China (www.savetrial.org). This will provide additional information to longitudinal cohorts [26] or short-term intervention studies [22]. Although there is growing evidence that CPAP is effective regarding sleepiness, daytime functioning and blood pressure, it is also obvious that most OSA chronic consequences may not be fully reversed by CPAP alone. However, it is difficult to randomise subjects for long-term

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studies, at least in severe OSA and specifically those presenting with the most severe sleepiness for ethical reasons. Actually, several RCTs were specifically targeted towards nonsleepy patients [25] or mild-to-moderate OSA patients (Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular Trial, protocol 06PRT/2675; principal investigator J. Stradling, Oxford University, Oxford, UK). None of these trials is fully completed and analysed although promising preliminary results have been presented in abstract form [28]. In any case, early intervention in stroke may represent a very specific model. As already mentioned, it is a difficult clinical condition for applying CPAP [14–17]. Specific strategies may also be applied. A study using auto-CPAP for two nights in TIA patients suggested that auto-CPAP was feasible in the acute phase of TIA and may reduce further vascular events [29]. Nevertheless, the evidence supporting OSA treatment in stroke patients is not strong enough to prevent promoting RCTs for ethical reasons. In addition, at least in selected individuals, it may represent an adequate target for randomisation, as clinical benefit may be obtained relatively rapidly (*i.e.* 1 month after stroke for neurological improvement [21]). Moreover, the other end-points (*e.g.* new cardiovascular events and cardiovascular mortality) might be submitted to intermediary analysis if needed. Most importantly, there is a scientific rationale to believe that early treatment of OSA in stroke patients may protect from further brain damage. There are data suggesting that pre-stroke lesions and white matter disease are associated with sleep-disordered breathing [30, 31]. Early use of CPAP may prevent recurrent hypoxaemia and cerebral flow fluctuations due to apnoea that could damage the area of ischaemic penumbra, thus affecting prognosis [32]. Suppressing further hypoxic insult may prevent stroke recurrence in at risk populations.

What is still to be done? The patients included in the study by PARRA *et al.* [21] are not representative of all stroke patients. Mortality was low, as more severe stroke patients were excluded. Also, the number of patients with minimal neurological dysfunction was high. Both may reflect the inclusion criteria: age <75 yrs, first episode of stroke, ischaemic stroke and enough consciousness to cooperate, and explain the low morbidity and mortality in the that series. Thus, such a RCT in a more severe population is certainly required. In addition, PARRA *et al.* [21] estimated that differences in mortality between the CPAP and control groups would be achieved if 100 patients had been included in each group. This also strongly suggests larger RCTs would show clearer differences in mortality. As previously mentioned, per protocol analysis was applied by PARRA *et al.* [21]. The same comment applies to the 5-yr Spanish RCT addressing new cardiovascular events including recurrent strokes [19]. Whilst a CPAP effect is obvious in per protocol analysis, having excluded the patients who did not tolerate CPAP, it is likely to be nonsignificant in intention-to-treat analysis. This does not mean that CPAP should not be proposed in the acute phase of stroke, but better pre-selection of candidates. This most certainly justifies large RCTs in unbiased stroke patient populations. Nevertheless, it is obvious that the present study will be considered in the future as an important piece of evidence.

STATEMENT OF INTEREST

None declared.

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