Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial

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Keywords
ischaemic stroke, mortality, nasal continuous positive airway pressure

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Accepted in revised form 15 May 2014; received 20 February 2013

DOI: 10.1111/jsr.12181

SUMMARY

The main purpose of the present analysis is to assess the influence of introducing early nasal continuous positive airway pressure (nCPAP) treatment on cardiovascular recurrences and mortality in patients with a first-ever ischaemic stroke and moderate–severe obstructive sleep apnea (OSA) with an apnea–hypopnea index (AHI) ≥20 events h^{-1} during a 5-year follow-up. Patients received conventional treatment for stroke and were assigned randomly to the nCPAP group (n = 71) or the control group (n = 69). Cardiovascular events and mortality were registered for all patients. Survival and cardiovascular event-free survival analysis were performed after 5-year follow-up using the Kaplan–Meier test. Patients in the nCPAP group had significantly higher cardiovascular survival than the control group (100 versus 89.9%, log-rank test 5.887; P = 0.015) However, and also despite a positive tendency, there were no significant differences in the cardiovascular event-free survival at 68 months between the nCPAP and control groups (89.5 versus 75.4%, log-rank test 3.565; P = 0.059). Early nCPAP therapy has a positive effect on long-term survival in ischaemic stroke patients and moderate–severe OSA.

INTRODUCTION

Sleep-related breathing disorders (SBD), and specifically obstructive sleep apnea (OSA), have been suggested to be a risk factor for stroke (Shahar *et al.*, 2001; Yaggi *et al.*, 2005) and an independent predictor of outcome in the affected patients in terms of functional recovery (Good *et al.*, 1996) and mortality (Parra *et al.*, 2004; Sahlin *et al.*, 2008).

Furthermore, in a recent randomized controlled study we have shown that early use of nasal continuous positive airway pressure (nCPAP) in patients with a first-ever ischaemic stroke with moderate–severe OSA [apnea–hypopnea index (AHI) ≥20 events h^{-1}] is associated with a significant improvement in neurological scales compared with the control group 1 month after stroke. Despite this better neurological initial recovery, cardiovascular recurrences and mortality were not significantly different between both groups when considered at 2-year follow-up probably, among other factors, because the follow-up was not long enough (Parra *et al.*, 2011).

The purpose of the present analysis is therefore to compare cardiovascular recurrences and mortality on a

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long-term basis between the two groups in this stroke patient setting, with an AHI $\geq$20 events h^{-1} (currently considered moderate–severe OSA, this associated with an increase in cardiovascular events) (Marin *et al*., 2005), assigned randomly to the nCPAP or control groups (Parra *et al*., 2011), in a 5-year follow-up.

PATIENTS AND METHODS

Design overview

A prospective, randomized, controlled, multi-centre study was designed to test the hypothesis that early nCPAP treatment in patients with moderate and severe OSA may affect outcome favourably in patients with a first-ever ischaemic stroke, in terms of neurological improvement, quality of life (Parra *et al*., 2011), occurrence of new cardiovascular events and mortality.

Setting and participants

Between September 2005 and December 2006, all patients with first-ever ischaemic stroke admitted consecutively to the Neurology Services of seven acute-care teaching hospitals throughout Spain were eligible. Inclusion criteria were age <75 years and at least one of the following conditions: habitual snoring, observed apneas or history of hypertension or a heart disease. Patients with consciousness impairment and patients previously diagnosed and treated for OSA were excluded. The protocol consisted of a complete neurological evaluation, assessment of cardiovascular risk factors, health-related quality of life as well as sleep studies. According to the respiratory polygraph (RP) evaluation, and based on AHI results, patients with AHI $\geq$ 20 were randomized to receive conventional treatment (described later) for stroke (control group) or conventional treatment plus nCPAP (nCPAP group), started in the acute stroke phase. All patients were followed initially for 24 months, a period in which patients from the nCPAP group remained with this respiratory device (Parra *et al*., 2011). Further telephone contact 5 years after the stroke provided data collection on survival and cardiovascular events for the present analysis.

The study was approved by the Institutional Review Boards of the participating centres. Written informed consent was obtained from all patients or their families.

Study procedures

Neurological and outcome data were recorded following the standardized protocol of the Hospital del Sagrat Cor Stroke Registry (Arboix *et al*., 1998). Stroke subtypes were classified according to the Cerebrovascular Study Group of the Spanish Society of Neurology (Arboix *et al*., 1998), including transient ischaemic attack, ischaemic stroke (atherothrombotic, cardioembolic, lacunar, unusual or undetermined origin) and intraparenchymatous haemorrhagic stroke. For the purpose of this study, only patients with ischaemic stroke were selected.

Functional abilities were assessed using the Barthel index (Mahoney and Barthel, 1965), a multi-faceted scale questionnaire that measures morbidity and daily living activities [0 (maximal disability) to 100 (no disability)], while maximal stroke severity or neurological impairment was estimated using the Canadian scale (Cote *et al*., 1986) [0 (maximal impairment) to 10 (no impairment)]. The modified Rankin scale (van Swieten *et al*., 1988) was used to assess outcome [scores ranging from 0 (no symptoms) to 6 (death)]; self-reported health status was assessed with the SF-36 Quality of Life questionnaire (Jenkinson *et al*., 1999).

Sleep studies

A sleep–wake habits and symptoms questionnaire consisted of 15 items; a four-grade Likert scale (never, rarely, sometimes, often and always) was applied within the first 48–72 h to assess snoring, observed apnea and hypersomnia in different situations. Details of the questionnaire have been reported previously by Parra *et al.* (2011), while daytime sleepiness was assessed with the Epworth Sleepiness Scale (Johns, 1991). All answers were obtained from patients themselves or, if needed, from their relatives.

A respiratory sleep study was performed in the ward during the first 48–72 h after admission with a portable respiratory recording device (Hypno TT Digital Recorder) that has been validated previously using full polysomnography in stroke patients (Parra *et al*., 2000). Respiratory nasal airflow (flow nasal sensory), chest wall movements (impedance), heart rate and thoracic impedance [electrocardiograph (ECG) electrodes], arterial oxygen saturation (SaO_2, finger pulse oximetry) and body position (position sensor) were also measured. Sleep-related breathing disorders were classified as obstructive or central apnea (cessation of airflow for $\geq$10 s with maintenance of thoracic motion or without any thoracic motion, respectively) or hypopnea (discernible reduction in airflow or thoracic motion lasting >10 s and associated with a cyclical dip in SaO2 of >3%). The AHI was calculated based on the time spent in bed with the respiratory recording device. Patients with an AHI $\geq$20 events h^{-1} of predominantly obstructive type (more than 80% of total count) were selected for randomization. In all cases, scoring of all these variables was performed manually by an experienced scorer, while the night-time percentage of SaO2 of <90% (CT90) was obtained automatically.

Randomization and intervention

Patients with an AHI $\geq$20 were randomized to receive conventional treatment for stroke plus nCPAP (nCPAP group) or conventional treatment without nCPAP (control group) using a computer-generated random list (1 : 1 ratio). Autotitration polygraphic studies were carried out using a validated portable system (Autoset Portable Plus II; ResMed,

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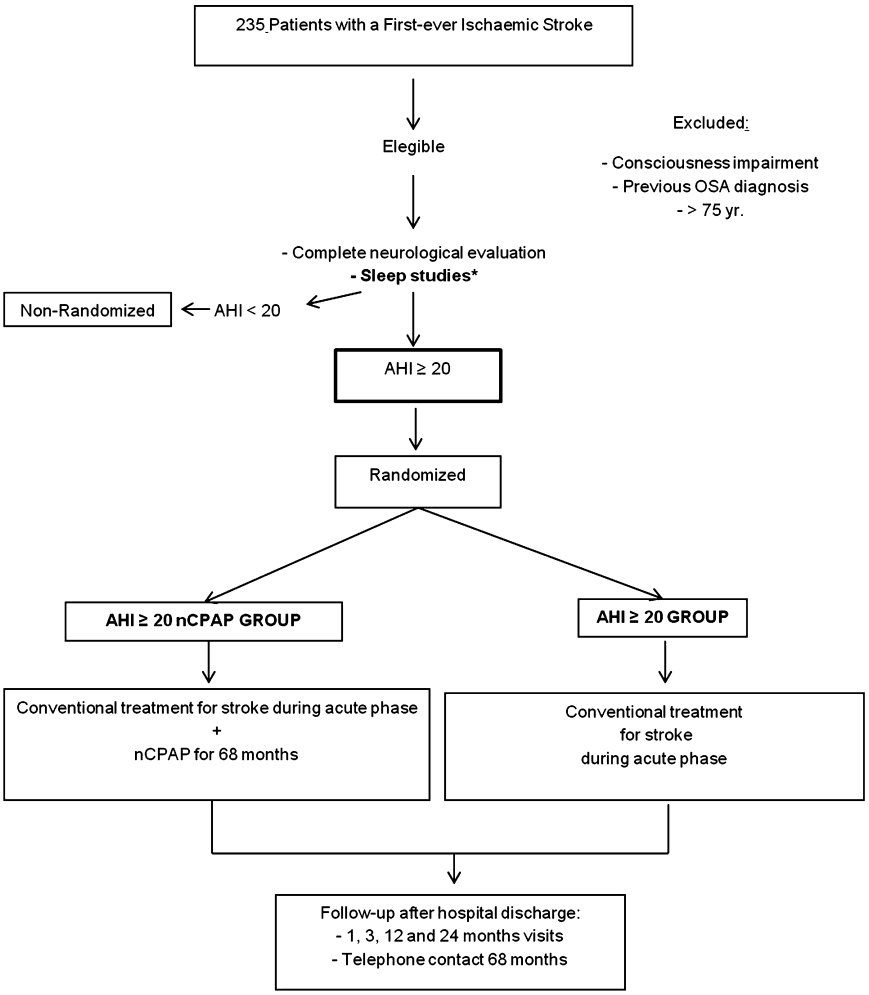
Sydney, Australia) (Molina *et al.*, 2003). Optimal pressure was determined visually on the raw data of the autoCPAP device ('view night profile'), analysing the pressure that included 90% of the periods with a leak lower than 0.4 L/s (90th percentile) normalized respiratory disturbances index (Masa *et al.*, 2004). Therefore, prescription with a fixed nCPAP was derived from examination of the profiles of pressure applied during autotitration CPAP.

In all patients assigned to the intervention arm, nCPAP was started during hospital admission between the first 3 and 6 days after stroke onset. In all cases, nCPAP was administered by well-trained nurses of the sleep units of the participating hospitals.

During the acute stroke phase, all patients were managed in accordance with the recommendations of the Spanish Cerebrovascular Study Group of the Spanish Society of Neurology (conventional treatment), as described previously by Arboix *et al.* (1998). The main strategies were: (i) maintenance of blood pressure without the use of hypotensive drugs (unless the systolic blood pressure was ≥ 220 mm Hg or the diastolic blood pressure ≥ 120 mm Hg); (ii) early treatment of hyperglycaemia avoiding the use of glucose infusion; (iii) prevention of pulmonary thromboembolism with low-dose heparin; and (iv) early antiplatelet therapy except when anticoagulation was recommended. Physical and respiratory therapies were also performed during the patients' stay in the hospital.

Outcomes and follow-up

After hospital discharge, patients were followed-up by a neurologist and a pneumologist at outpatient clinics at 1, 3, 12 and 24 months after stroke. At all visits, evaluations included a physical examination and the administration of the Barthel index, Canadian scale, Rankin scale and SF-36. Patients who received nCPAP during the acute stroke phase were prescribed to continue with the respiratory device. Compliance with nCPAP was considered adequate when the system counter registered more than 4 h per night (70% of the days) and was checked during all medical visits



* Respiratory sleep study within 48–72 h of admission was performed with a portable respiratory recording device. Apnea-Hypopnea Index (AIH) was scored manually by an experienced scorer based on the results registered during the test. OSA: Obstructive Sleep Apnea; yr: years old; nCPAP: nasal Continuous Positive Airway Pressure

Figure 1. Flowchart of the study population.

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undertaken during the first 24 months of the study. Patients were recommended to continue with the respiratory device based on the pneumologist criteria and clinical patient characteristics.

Cardiovascular events including cardiac ischaemic events, stroke recurrence and cardiovascular mortality were recorded during the study visits (the first 24 months) and through post-visit telephone contact at the end of the study for every patient (median follow-up of 68 months).

Statistical analysis

A per-protocol analysis was carried out, excluding those patients who declined nCPAP during hospitalization.

Baseline characteristics were analysed using descriptive statistics. Categorical variables are presented in the form of lists and proportions, while for quantitative variables (continuous or ordinal) indices of central tendency (mean) and dispersion [standard deviation (SD)] are also presented. Comparison between groups was performed with Pearson's chi-squared test.

Survival analysis for each group was estimated using Kaplan–Meier survival curves, considering the length of time after randomization until occurrence of cardiovascular events, survival probability estimates at 5-year and cardiovascular mortality. Significance was set at $P < 0.05$. All data statistical analysis was made using SPSS for Windows.

RESULTS

The study sample comprised a total of 235 patients with a first-ever ischaemic stroke.

Table 1 Baseline characteristics

	nCPAP group (n = *57)*	*Control group* (n = *69)*	P-*value**
Sex, men/women	41/16	48/21	0.772
Age, years, mean (SD)	63.7 (9.1)	65.5 (9.1)	0.264
Body mass index (BMI), kg m^2, mean (SD)	30.2 (4.6)	28.8 (4.0)	0.093
Neck circumference, cm, mean (SD)	41.9 (3.8)	42.3 (4.2)	0.671
Snoring (often or always)	54 (94.7)	59 (85.5)	0.090
Respiratory data			
Observed apnea at night (often or always)	40 (70.2)	32 (46.4)	<0.01
Epworth Sleepiness Scale, score, mean (SD)	8.3 (3.3)	7.3 (4.1)	0.156
Vascular risk factors			
Hypertension	33 (60)	43 (63.2)	0.714
Diabetes mellitus	21 (38.2)	25 (36.8)	0.872
Atrial fibrillation	2 (3.6%)	6 (8.8%)	0.246
Ischaemic heart disease	7 (12.7)	12 (17.6)	0.453
Chronic obstructive pulmonary disease	3 (5.9)	5 (7.4)	0.671
Dyslipidaemia	26 (47.3)	21 (30.9)	0.063
Smoking	25 (45.5)	22 (32.4)	0.137
Alcohol abuse	12 (21.8)	6 (8.8)	<0.05
Salient clinical features			
Sudden onset	19 (33.9)	24 (35.3)	0.874
Headache	7 (12.5)	4 (5.9)	0.197
Motor deficit	32 (57.1)	37 (54.4)	0.761
Sensory deficit	19 (33.9)	21 (30.9)	0.718
Speech disturbances	14 (25.0)	25 (36.8)	0.160
Stroke subtypes			
Atherothrombotic	26 (47.3)	27 (41.5)	0.529
Cardioembolic	6 (10.9)	8 (12.3)	0.812
Lacunar	21 (38.2)	29 (44.6)	0.476
Unusual cause	1 (1.8)	2 (3.1)	0.660
Undetermined etiology	0	3 (4.6)	0.107
Neurological assessment			
Barthel index, mean (SD)	75.9 (27.9)	73.6 (27.0)	0.653
Canadian scale, mean (SD)	8.3 (1.6)	8.0 (1.9)	0.393
Rankin scale, mean (SD)	2.3 (1.3)	2.8 (1.3)	0.055
Quality of life, SF-36, mean (SD)			
Physical component summary	42.3 (11.1)	43.2 (9.8)	0.671
Mental component summary	47.1 (13.3)	48.2 (12.9)	0.664

nCPAP group: patients with apnea–hypopnea index (AHI) ≥ 20 with conventional treatment for stroke + nasal continuous positive airway pressure; control group: patients with AHI ≥ 20 with conventional treatment for stroke; *P*-value: Pearson's chi-squared test; SD, standard deviation.
*Significance at $P < 0.05$.

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Sleep studies allowed the classification of patients as AHI<20 (n = 95) or AHI≥20 (n = 140). After randomization, and exclusion of patients who initially refused nCPAP (n = 14) the final study sample comprised 57 patients assigned to the nCPAP group and 69 patients for the control group (Parra *et al.*, 2011) (Fig. 1).

Baseline characteristics of both intervention groups were similar for sociodemographics, salient clinical features of stroke, frequency according to stroke subtypes, neurological assessment and quality of life, except for 'often observed apnea at night' (nCPAP 70.2 versus 46.4% in the control group; $P \leq 0.01$) and regarding alcohol abuse as a cardiovascular risk factor (21.8 versus 8.8%; $P \leq 0.05$), which were also significantly more frequent in the nCPAP group (Table 1).

The mean (SD) number of hours with nCPAP after stroke was 5.3 (1.9) per night, during a mean of 6.8 (0.6) nights per week. Further data on nCPAP adherence and compliance are detailed extensively in our previous paper (Parra *et al.*, 2011).

Survival

Cardiovascular survival (excluding non-cardiovascular deaths) after a mean of 68 follow-ups was 89.9% (62 of 69) in the control group and 100% (57 of 57) in the nCPAP group, with a log-rank test 5.887, statistically significant difference P = 0.015 (Fig. 2).

Cardiovascular event-free survival (cardiovascular events + cardiovascular deaths) after 68 months was lower in the control group, 75.4% (52 of 69), than in the nCPAP group, 89.5% (51 of 57), but this difference was not statistically significant (log-rank test 3.565; P = 0.059) (Fig. 3)

Non-cardiovascular deaths comprised four cancer cases (one in the control group and three in the nCPAP group), three respiratory deaths (all three in the nCPAP group) and one renal failure in the control group (Table 2), with no differences between both groups.

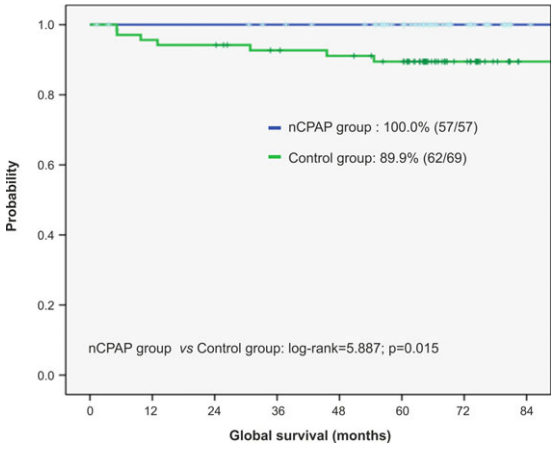

Figure 2. Cardiovascular survival [nasal continuous positive airway pressure (nCPAP) group and control group].

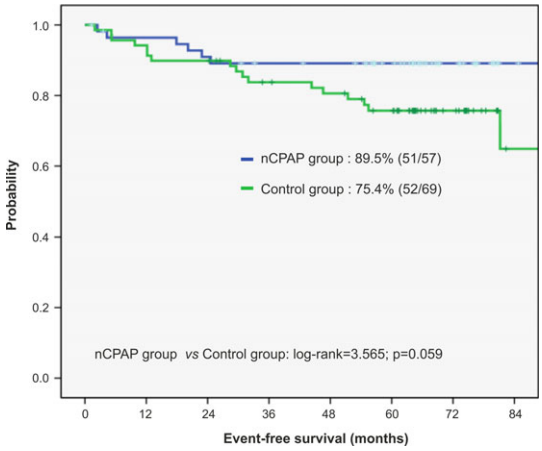

Figure 3. Cardiovascular event-free survival [nasal continuous positive airway pressure (nCPAP) group and control group].

Table 2 Outcome: cardiovascular events and mortality

5-year follow-up

	nCPAP group (n = 57)	Control group (n = 69)
Cardiovascular events		
Stroke	3	8
Transient ischaemic attack	1	1
Angina	1	1
Myocardial infarction	1	0
Other events	0	0
Deaths	6	9
Cardiovascular-related deaths	0	7
Non-cardiovascular-related deaths	6	2

DISCUSSION

In this study we compared patients with a first-ever ischaemic stroke and selected those who, by means of RP, are considered as having moderate–severe OSA (AHI ≥ 20), and who were randomized to be treated or not with nCPAP during the acute stroke phase with maintenance of the respiratory device at long-term (5-year follow-up). Our present results suggest that stroke patients in such a setting, when treated with early nCPAP treatment, not only have a better neurological recovery (Parra *et al.*, 2011), but also higher cardiovascular survival at 5-year follow-up compared to the control group.

The presence of obstructive events has been suggested previously as a risk factor with harmful consequences in stroke patients (Shahar *et al.*, 2001; Yaggi *et al.*, 2005), but also as a possible prognostic factor based on its known physiopathological mechanisms, although this relation has not been demonstrated fully (Balfors and Franklin, 1994; Drager *et al.*, 2005; Minoguchi *et al.*, 2005; Schulz *et al.*, 2002). The results of our previous study also point in this

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direction (Parra *et al*., 2004). In spite of the known increase in obstructive respiratory events through age, it has often been difficult to establish their clinical relevance and influence on stroke, a condition that usually occurs in elderly patients. Previous studies have shown that sleep-related breathing disorders in elderly people are frequent, and could also have a deleterious impact for this age group (Muñoz *et al*., 2006).

The randomization to nCPAP for patients with AHI $\geq$ 20 was carried out based not only on the association of this condition with high mortality in elderly people (Ancoli-Israel *et al*., 1991), but also considering some possible limitations of RP for the determination of AHI. Despite the advantages of RP as a tool for early bedside evaluation in this particularly difficult setting of stroke patients, previously documented limitations such as underestimation of AHI and a higher variability in AHI, especially at low values (<20 or even <30 depending on the studies) (Masa *et al*., 2011), led us to consider a cutoff point at AHI $\geq$ 20 to ensure that the group could benefit from nasal CPAP treatment based on current knowledge.

Our findings suggest that, in this setting, administration of nCPAP might be advisable at least when moderate–severe OSA is demonstrated in a stroke patient, which is a quite prevalent condition in this group of patients (Parra *et al*., 2000). Clearly, neurological recovery from stroke and short- or long-term survival depend upon a variety of factors, not only on reducing the frequency of obstructive events, with notable improvements since managing such patients in specialized stroke units. However, and based on our results, we consider that OSA are among the factors that should be considered and controlled.

Our findings are also supported by the results of a recent paper that recommends treatment with automatic nCPAP even before determining the presence of apneas; in that case, nCPAP was withdrawn when the subsequent polysomnography study indicated that the number of apneas was not abnormally high (Bravata *et al*., 2011). Although this approach is perhaps excessive, our study provides new data in support of nCPAP in stroke patients and, importantly, corroborates other studies suggesting that there is no risk to the patient (Bravata *et al*., 2011; Parra *et al*., 2011). Naturally, patients must be selected carefully to ensure that compliance with treatment will be satisfactory in the acute phase; the results presented here should not be extrapolated to more serious cases of stroke in which the feasibility of treatment is not guaranteed.

In terms of survival, although no significant differences were observed between groups in our previous 2-year follow-up study (Parra *et al*., 2011), due probably to a low mortality rate regarding the non-severe characteristics of the studied sample (age 75 years, first episode of stroke and ischaemic stroke and consciousness to cooperate) and a limited follow-up period, our current findings show that after a median follow-up of 68 months, the nCPAP group had significantly higher cardiovascular survival and a higher cardiovascular event-free survival in comparison to the control group.

Therefore, our current results suggest that nCPAP therapy has a positive effect on the long-term survival in patients with ischaemic stroke. Moreover, early nCPAP treatment in ischaemic stroke patients might be beneficial not only in initial neurological recovery, but to prevent cardiovascular events on a long-term basis.

In summary, obstructive apneas have a negative effect on neurological recovery in patients with ischaemic stroke. In our current study a higher cardiovascular survival was obtained in patients with nasal CPAP. Ongoing research should explore this issue in more depth. In the future, efforts should be made in order to define the group of patients with ischaemic stroke who can benefit of this treatment.

ACKNOWLEDGEMENTS

This study was supported in part by grants from FIS PI08/1514, PI05/0678, PI05/2631, and PI05/0772 Madrid, Spain. OP, AA, JD-C, JGM and MLA belong to CIBER de Enfermedades Respiratorias (CibeRes-CB06/06), Ministerio de Ciencia e Innovación, Madrid, Spain.

CONFLICT OF INTEREST

No conflicts of interest declared.

REFERENCES

Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R. and Kaplan, O. Sleep disordered breathing in community-dwelling elderly. *Sleep*, 1991, 14: 486–495.

Arboix, A., Alvarez-Sabin, J. and Soler, L. for the Cerebrovascular Study Group of the Spanish Society of Neurology. Nomenclatura de las enfermedades vasculares cerebrales. *Neurologia*, 1998, 13: 1–10.

Balfors, E. M. and Franklin, K. A. Impairment of cerebral perfusion during obstructive sleep apneas. *Am. J. Respir. Crit. Care Med*., 1994, 150: 1587–1591.

Bravata, D. M., Concato, J., Fried, T. *et al.* Continuous positive airway pressure: evaluation of a novel therapy for patients with acute ischemic stroke. *Sleep*, 2011, 34: 1271–1277.

Cote, R., Hachinski, V. C., Shurvell, B. L., Norris, J. W. and Wolfson, C. The canadian neurological scale: a preliminary study in acute stroke. *Stroke*, 1986, 17: 731–737.

Drager, L. F., Bortolotto, L. A., Lorenzi, M. C., Figueiredo, A. C., Krieger, E. M. and Lorenzi-Filho, G. Early signs of atherosclerosis in obstructive sleep apnea. *Am. J. Respir. Crit. Care Med*., 2005, 172: 613–618.

Good, D. C., Henkle, J. Q., Gelber, D., Welsh, J. and Verhulst, S. Sleep-disordered breathing and poor functional outcome after stroke. *Stroke*, 1996, 27: 252–259.

Jenkinson, C., Davies, R., Mullins, R. and Stradling, J. R. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnea a randomised prospective parallel trial. *Lancet*, 1999, 353: 2100–2105.

Johns, M. W. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*, 1991, 14: 540–545.

Mahoney, F. I. and Barthel, D. W. Functional evaluation: the Barthel Index. *Md. State Med. J*., 1965, 14: 61–65.

Marin, J. M., Carrizo, S. J., Vicente, E. and Agusti, A. G. Long-term cardiovascular outcomes in men with obstructive sleep apnea

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hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*, 2005, 365: 1046–1053.

Masa, J. F., Jiménez, A., Durán, J. *et al.* Alternative methods of titrating continuous positive airway pressure: a large multicenter study. *Am. J. Respir. Crit. Care Med*., 2004, 170: 1218–1224.

Masa, J. F., Corral, J., Pereira, R. *et al.* Therapeutic decision-making for sleep apnea and hypopnea syndrome using home respiratory polygraphy. *Am. J. Respir. Crit. Care Med*., 2011, 184: 964–971.

Minoguchi, K., Yokoe, T., Tazaki, T. *et al.* Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. *Am. J. Respir. Crit. Care Med*., 2005, 172: 625–630.

Molina, M., Hernandez, L., Duran, J. *et al.* Protocol to evaluate automatic continuous positive airway pressure. Assessment of the usefulness of the Autoset-T device to determine optimal pressure for treating sleep apnea/hypopnea syndrome. *Arch. Bronconeumol*., 2003, 39: 118–125.

Muñoz, R., Duran-Cantolla, J., Martinez-Vila, E. *et al.* Severe sleep apnea and risk of ischemic stroke in the elderly stroke patient. *Stroke*, 2006, 37: 2317–2321.

Parra, O., Arboix, A., Bechich, S. *et al.* Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am. J. Respir. Crit. Care Med*., 2000, 161: 375–380.

Parra, O., Arboix, A., Montserrat, J. M., Quinto, L., Bechich, S. and Garcia-Eroles, L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur. Respir. J*., 2004, 24: 267–272.

Parra, O., Sanchez-Armengol, A., Bonnin, M. *et al.* Early treatment of obstructive apnea and stroke outcome: a randomised controlled trial. *Eur. Respir. J*., 2011, 37: 1128–1136.

Sahlin, C., Sandberg, O., Gustafson, Y. *et al.* Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. *Arch. Intern. Med*., 2008, 168: 297–301.

Schulz, R., Hummel, C., Heinemann, S., Seeger, W. and Grimminger, F. Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. *Am. J. Respir. Crit. Care Med*., 2002, 165: 67–70.

Shahar, E., Whitney, C. W., Redline, S. *et al.* Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am. J. Respir. Crit. Care Med*., 2001, 163: 19–25.

van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H. J. and van Gijn, J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, 1988, 19: 604–607.

Yaggi, H. K., Concato, J., Kernan, W. N., Lichtman, J. H., Brass, L. M. and Mohsenin, V. Obstructive sleep apnea as a risk factor for stroke and death. *N. Engl. J. Med*., 2005, 353: 2034–2041.

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