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Early treatment of obstructive apnea and stroke outcome: a randomized controlled trial

Short title: Early CPAP and stroke outcome.

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Abstract (word count 200)

Question of the study: To assess the impact of nasal continuous positive airway pressure (nCPAP) in ischemic stroke patients followed for 2 years.

Materials/patients and methods: Stroke patients with an apnea-hypopnea index ≥20 were randomized to early nCPAP (n = 71) (3–6 days of stroke onset) or conventional treatment (n = 69). The Barthel Index, the Canadian Scale, the Rankin Scale, and the SF-36 were measured at baseline and at 1, 3, 12, and 24 months.

Results: The percentage of patients with neurological improvement 1 month after stroke was significantly higher in the nCPAP group (Rankin scale 90.9% *vs* 56.3%, $P < 0.01$; Canadian scale 88.2% *vs* 72.7%, $P < 0.05$). The mean time until the appearance of cardiovascular events was longer in the nCPAP group (14.9 *vs* 7.9 months, $P = 0.044$), although cardiovascular events free survival after 24 months was similar in both groups. The cardiovascular mortality rate was 0% in the nCPAP group and 4.3% in the control group ($P = 0.161$).

Answer to the question: Early use of nCPAP seems to accelerate neurological recovery and to delay the appearance of cardiovascular events, although an improvement in patients' survival or quality of life was not shown.

The study protocol was registered at ClinicalTrials.gov Protocol Registration System (PRS) and the number assigned was NCT00202501.

Keywords: Cardiovascular events, ischemic stroke, nasal continuous positive airway pressure, neurologic outcome, quality of life, mortality.

Introduction

Sleep-related breathing disorders are associated with an increase in cardiovascular morbidity and mortality in general [1–3]. Sleep disordered breathing occurs frequently in stroke patients [4–6]. It has been shown that obstructive sleep apnea (OSA) is a risk factor for stroke [7,8] and an independent predictor of outcome in terms of functional recovery [9] and mortality [10,11]. Because there are data in favor of the physiopathologic plausibility of this association [12–15], it seems reasonable to perform intervention studies of treatment with continuous positive airways pressure (CPAP) in stroke patients. Nasal CPAP (nCPAP) is the most effective treatment for OSA [16,17] and for OSA-associated hypertension [18–21], which has been suggested to act on the underlying mechanisms by which OSA increases the risk of stroke [22–24].

Because stroke and sleep-related breathing disorders are frequent and interrelated conditions, with a deleterious impact in older people [25], the possibility to demonstrate a favorable effect of treatment with nCPAP could be great of social and economic importance. In fact, clinical data available to date regarding the use of nCPAP in the management of stroke patients with OSA are still scarce and controversial [26–28], with both encouraging [29] and disappointing results [30–33]. In a recent open-label 5-year follow-up study of stroke patients with moderate-severe sleep apnea, nCPAP treatment started in the stable phase of the disease was associated with a reduction in the excess risk of mortality found in OSA patients with stroke [34].

To shed light on literature discrepancies, we explored the robustness of previous findings in patients with first-ever ischemic stroke and OSA using a randomized controlled design. The objectives of the study were: a) to assess the benefits at 2 years of early nCPAP treatment on functional outcome, quality of life, appearance of new

cardiovascular events and mortality, and b) to assess the feasibility of using nCPAP in the early phase of stroke.

Patients and methods

Design overview

A prospective, randomized, controlled and multicenter study was designed to test the hypothesis that early nCPAP treatment may affect favorably the outcome of patients with first-ever ischemic stroke in terms of neurologic improvement, quality of life, occurrence of new cardiovascular events, and mortality.

Setting and participants

Between September 2005 and December 2006, all patients with first-ever ischemic 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 ischemic heart disease. Patients with consciousness impairment and patients previously diagnosed and treated for OSA were excluded. The protocol consisted of complete neurologic assessment, cardiovascular risk factors, health-related quality of life, and sleep studies. Patients with moderate-severe sleep apnea defined by an apnea-hypopnea index (AIH) ≥20 were randomized to receive conventional treatment (later described) for stroke plus nCPAP (nCPAP group) or conventional treatment without nCPAP (control group) during the acute phase of stroke and were followed for 24 months.

The study was approved by institutional review boards of the participating centers and written informed consent was obtained from all patients or their families.

Study procedures

Neurologic and outcome data were recorded following the standardized protocol of the Hospital del Sagrat Cor Stroke Registry [35]. Stroke subtypes were classified according to the Cerebrovascular Study group of the Spanish Society of Neurology [36] and include transient ischemic attack; ischemic stroke, either atherothrombotic, cardioembolic, lacunar, unusual or undetermined origin; and intraparenchymatous hemorrhagic stroke. For the purpose of this study, patients with ischemic stroke were selected.

Functional abilities were assessed by the Barthel index [37], a multifaceted scale questionnaire that measures morbidity and daily living activities (scores ranges from 0 [maximal disability] to 100 [no disability]), where a score < 20 indicates that the person is totally dependent, a score between 20 and 35, a severe level of disability, a score between 40 and 55 a moderate level of disability, a score ≥ 60 a mild level of disability, and 100 no disability or that the person is totally independent. The maximal severity of stroke or neurological impairment was estimated with the Canadian scale [38] (total score ranges from 0 [maximal impairment] to 10 [no impairment]). The modified Rankin scale [39] was used to assess outcome (scores ranges from 0 [no symptoms] to 6 [death]). Self-reported health status was assessed with the SF-36 quality of life questionnaire [40]. The physical (PCS-36) and the mental (PCS-36) component summaries were calculated.

Sleep studies

A sleep-wake habits and symptoms questionnaire that consisted of 15 items including snoring, observed apnea, and hypersomnia in different situations was applied within the first 48–72 h. The possible answers were never, rarely, sometimes, often, and always.

Details of the questionnaire have been previously reported [6]. Daytime sleepiness was also assessed with the Epworth Sleepiness Scale [41]. Answers were obtained from the patients themselves or with the aid of relatives if needed.

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 have been previously validated using full polysomnography and used in stroke patients [6]. Respiratory nasal airflow (flow nasal sensory), chest wall movements (impedance), heart rate and thoracic impedance (ECG electrodes), arterial oxygen saturation (SaO_2, finger pulse oximetry), and body position (position sensor) were measured. Sleep-related breathing disorders were classified as obstructive or central apnea, with apnea considered a cessation of airflow for ≥ 10 s with maintenance of thoracic motion or without any thoracic motion, respectively. A hypopnea was considered a discernible reduction in airflow or thoracic motion which lasted > 10 s and was associated with a cyclical dip in SaO2 of > 3%. The AHI was calculated taken into account the time spent in bed with the respiratory recording device. In all cases, scoring of these variables was performed manually by an experienced scorer. The percentage of night-time with SaO2 of < 90% (CT90) was obtained automatically.

Randomization and intervention

Patients with an AHI ≥ 20 (with predominantly obstructive events) were randomized to receive conventional treatment for stroke plus nCPAP or conventional treatment without nCPAP (control group) using a computer-generated random list (1:1 ratio). Auto-titration polygraphic studies were carried out using a validated portable system (Autoset Portable Plus II, ResMed, Sydney, Australia) [42]. The optimal pressure was determined visually on the raw data of the autoCPAP device (“view night profile”) by

analyzing the pressure that included 90% of the periods with a leak lower than 0.4 L/s (90th percentile), providing the pressure that normalizes respiratory disturbances index [43]. Therefore, a fixed nCPAP prescribed was derived from examination of the profiles of the pressure applied during auto-titration CPAP.

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

In the acute phase of stroke, patients were managed in accordance with recommendations of the Spanish Cerebrovascular Study Group of the Spanish Society of Neurology as previously described [36]. Main strategies were as follows: (a) 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; (b) early treatment of hyperglycemia avoiding the use of glucose infusion; (c) prevention of pulmonary thromboembolism with low-dose heparin; and (d) early antiplatelet therapy except when anticoagulation was recommended. Physical and respiratory therapy was performed during the patient's stay in the hospital.

Outcomes and follow-up

After hospital discharge, patients were followed by a neurologist and a pneumologist at the outpatient clinics at 1, 3, 12, and 24 months after stroke. In all visits, a physical examination was performed, and the Barthel index, Canadian scale, Rankin scale, and SF-36 were administered. nCPAP treatment was considered adequate when the system counter registered more than 4 h (70%) of the days) per night, checked during all medical visits undertaken during the study. Cardiovascular events including cardiac

ischemic events, stroke recurrence, and cardiovascular mortality were recorded during the study visits and asked by phone at the end of the study for every patient.

Statistical analysis

A per-protocol analysis was carried out, so that patients who refused nCPAP during hospitalization were excluded. A descriptive study of baseline characteristics of the study sample was performed. To check the homogeneity of the study groups, we performed between-group comparisons (OSA group with nCPAP versus OSA group without nCPAP) with regard to demographic data, sleep-related data, respiratory polysomnography and neurological data, using one-factor analysis of variance (ANOVA) and the Pearson's (χ^2) chi-square tests. Mean scores of the Barthel index, Canadian Scale, Rankin scale, and SF-36 at 1, 3, 12 and 24 follow-up months were compared with baseline data (except for SF-36 in which the last three visits were compared with visit at 1 month) were compared with the Student's *t* test for paired samples and between groups with one-factor ANOVA. Improvement variables of neurological scales included the following: improvement of the Barthel index (improvement in the level of disability or no disability from the beginning), improvement of the Rankin scale (reduction of $\geq$ 1 point or score 0 from the beginning), and improvement in the Canadian scale (increases of $\geq$ 5 points or score 10 from the beginning). The percentage of patients that showed an improvement in the neurological scales at 1 month after stroke in both groups was compared with the Pearson's (χ^2) chi-square test and the odds ratio (OR) calculation.

To study the incidence of exitus (overall mortality), cardiovascular death (cardiovascular mortality), and the incidence of cardiovascular events (including cardiac ischemic events, stroke recurrence, and cardiovascular death) we used univariate tests

for the comparison of proportions (χ^2 tests and calculation of OR). Moreover, the time elapsed from the onset of stroke to the appearance of cardiovascular events in both groups was compared with the Z Kolmogorov-Smirnov test.

Direct survival analysis of the cardiovascular events, including stroke recurrence and/or cardiovascular exitus were also performed using Kaplan-Meier tests.

To evaluate the related factors we performed univariate tests ((χ^2 tests and calculation of OR) and multivariable analyses with Cox proportional-hazards regression model which included, in addition to the study group (nCPAP or control group), the AHI, CT90, factors such as sex, age, BMI, history of hypertension, ischemic heart disease, smoking, body mass index, and scores on the Barthel, Canadian, ESS, and Rankin scales. Significance was set at $P < 0.05$. The SPSS (version 13.0 for Windows) was used for statistical analysis.

Results

Of a total of 235 patients with first-ever ischemic stroke recruited during the study period and undergoing a respiratory sleep study during the acute phase of stroke, 140 met the criteria of AHI $\geq$ 20 and were randomized to the group of treatment with nCPAP (n = 71) or to the control group (n = 69). However, 20 of the 71 patients (28.2%) in which nCPAP treatment was started refused nCPAP due to machine discomfort (14 patients were excluded because of nCPAP refusal after 1 to 3 nights of treatment and the remaining 6 patients not excluded during their hospital stay refused nCPAP at follow-up after a mean of 10 months of treatment). Therefore, the study population consisted of 57 patients assigned to the nCPAP group and 69 to the control group (Figure 1). Treatment with nCPAP was started at a mean (SD) of 4.6 (2.8) days after the onset of stroke.

Patients in both study groups showed similar baseline characteristics (Table 1). The groups were balanced in terms of drugs administered in the hospital acute phase. The baseline characteristics of the 14 patients excluded from the study because of refusal of nCPAP during hospitalization were similar to those of the whole study population. The mean (standard deviation, SD) length of hospital stay was 8.7 (4.3) days in the nCPAP group and 9.3 (4.6) in the control group, without statistically significant differences. There were no in-hospital deaths and all patients were discharged alive from the hospital.

Patients were followed for a mean (SD) of 23.04 (3.7) months. The mean (SD) number of hours of nCPAP use was 5.3 (1.9) per night during a mean of 6.8 (0.6) nights per week. The mean nCPAP pressure was 8.6 (1.5) cm H_2O. Face mask was necessary in only 4 patients because of leaks mainly due to facial palsy.

In both groups, there were significant changes in the Barthel, Canadian, and Rankin scales in all visits as compared with baseline (Figure 2). The percentage of patients with improvements in the neurological assessments 1 month after stroke was significantly higher in the nCPAP group than in controls in the Rankin scale (90.9% *vs* 56.3%, $P < 0.01$, OR = 7.8) and the Canadian scale (88.2% *vs* 72.7%, $P < 0.05$, OR = 2.8), even when patients with less severe neurological impairment (baseline score in the Rankin scale = 1 and baseline score in the Canadian scale = 10) were excluded. However, significant differences in the percentage of patients with improvements in the Barthel index were not observed (Table 2). Although almost all mean scores of the neurological scales and the physical and mental component summaries of the SF-36 were better in the nCPAP group in all follow-up visits, statistically significant differences were not observed (Table 3).

Outcome in terms of mortality and new cardiovascular events (including stroke recurrence and cardiovascular deaths) are shown in Table 4. The cardiovascular mortality rate was 0% in the nCPAP group (n = 0) compared with 4.3% in the control group (n = 3) (P = 0.161). The rate of cardiovascular events (including cardiac ischemic events, stroke recurrence, and cardiovascular death) was 12.3% (7/57) in the nCPAP group and 11.6% (8/69) in the control group (P = 0.560). The mean time from stroke onset until the appearance of the first cardiovascular event was significantly longer in the nCPAP group than in the control group (14.9 *vs* 7.9 months, P = 0.044). The overall free-cardiovascular event survival rate after 24 months was 87.7% (50/57) in the nCPAP group and 88.4% (61/69) in the control group (log-rank test 0.01, P = 0.911) (Figure 3).

In the univariate and multivariable analysis of factors associated with cardiovascular events or mortality at follow-up, none of the variables analyzed, included sex, age, body mass index, snoring, observed apnea, history of hypertension, ischemic heart disease, smoking, dyslipemia, Epworth Sleepiness scale, Barthel index, Canadian scale, Rankin scale, AHI, CT90, and nCPAP were associated with a higher risk (variable nCPAP, hazard ratio 0.62, 95% confidence interval 3.46−0.11, P =0.586).

Discussion

The present results indicate that early use of nCPAP in patients with a first-ever ischemic stroke and moderate-severe OSA is associated with a significant improvement in the assessment of neurological scales at 1 month after stroke in the nCPAP group compared with controls, whereas in the subsequent follow-up visits, although more favorable results were obtained in the nCPAP group, differences were not significant, probably because patients in both groups were already recovered from the acute phase

of stroke. Acceptance of nCPAP therapy and adherence to treatment were highly acceptable despite the fact that nCPAP was started early in the acute phase of stroke. After a follow-up of 24 months, a significant increase in the length of time until the appearance of cardiovascular events (almost double) in the nCPAP group, a low cardiovascular mortality (no case of cardiovascular death versus 3 deaths in the control group), although without statistically significant differences, and a cardiovascular events free survival similar than in control patients. To our knowledge, this is the first study of early nCPAP carried out in a homogeneous group of patients with acute first-ever ischemic stroke. Patients with recurrent stroke would present a more severe clinical condition, presumably due to previous neurological deficits which would affect the follow-up of these cases, and for this reasons patients with previous stroke were excluded. On the other hand, randomized controlled studies of nCPAP therapy in acute stroke patients introduced within the first days after stroke onset and assessing quality of life, in addition to neurological outcome, recurrence of cardiovascular events and mortality have not previously been reported.

Different studies have analyzed the influence of sleep-related breathing disorders as cardiovascular [1–3] and cerebrovascular [7,8] risk factors as well as the prognostic implications of OSA [9–11]. In this sense, we choose AHI $\geq$ 20 because an excess of mortality has been previously described in elderly people [44] and also because using respiratory polygraphy the AHI can be underestimated. However, a few studies have assessed systematically the effect of nCPAP therapy. Studies with more promising results [26−29] are non-controlled observational evaluations of clinical series of patients, with an adherence rates lower than 50%, poorly defined outcomes, assessments carried out at different time points during the clinical course of stroke, and lack of mid- or long-term follow-up data. On the other hand, less encouraging studies have been

reported either by the absence of significant differences between nCPAP and non-nCPAP groups in a small number of patients or by the total inability of using nCPAP in the acute phase of stroke [30–33]. Reviews of OSA and the risk of stroke have repeatedly claimed the need for randomized controlled trials [45].

It is generally believed that nCPAP treatment in stroke patients is difficult, particularly in the acute phase of stroke during in-hospital care. Although it may be argued that in our study severe stroke patients were probably excluded because only first-ever stroke patients with unaltered level of consciousness were eligible, encouragement and full explanation of the usefulness of nCPAP were positive drivers to obtain non-compliance rates at follow-up which are similar to those reported in patients OSA syndrome [46]. On the other hand, and in order to facilitate adherence to nCPAP, age under 75 years was an inclusion criterion, which probably accounted for the exclusion of stroke patients with a more severe condition as shown by the low mortality rate observed in this cohort. Although one concern is choosing the moment for starting nCPAP treatment given neurological deficits, including facial palsy, and impaired psychological status of stroke patients immediately after stroke, early use of nCPAP may prevent recurrent hypoxemia and flow cerebral fluctuations due to apnea that could damage the area of ischemic penumbra and therefore, affect prognosis [47]. In this case, nCPAP could exert a beneficial influence in the acute phase. The lack of somnolence in these patients in another factor that may account for poor adherence. The fact that placebo nCPAP was not used is a limitation of the study. A per-protocol analysis was carried out and for this reason, the 14 patients who refused nCPAP during hospitalization were excluded. Although and intention-to-treat analysis would be perhaps a more rigorous approach, the plausibility that including such patients in the nCPAP group would improve nCPAP results is really poor. However, the other 6

patients who had poor tolerance to nCPAP with a mean use of 10 months were maintained in the group, but no differences were observed when data were reanalyzed excluding these patients.

The present findings have shown a favorable effect of nCPAP on the short-term neurological recovery (1 month) but no significant differences were found in the subsequent follow-up visits, although a constant trend in almost all parameters analyzed to obtain a higher improvement in patients with nCPAP was observed. It may be hypothesized that differences may be more evident with a larger sample size but it seems that benefits of nCPAP may appear in stroke patients with a more severe condition, rather than with a higher number of cases. It was found that excluding patients with less severe neurological impairment, results at 1 month were consistently significant despite a reduction in the number of patients.

Another possibility is that the parameters used to assess patient's outcome, which were mainly clinical, may not be sufficiently sensitive. Stroke measures used in this study have been criticized for the low sensitivity in patients with minor stroke. In the case of the Barthel scale a "ceiling effect" of 64.6% in patients with minor stroke and of 24.8% in patients with moderate stroke has been reported [48], which may probably account for the inconclusive results in the Barthel index obtained in this study. It is possible that the evaluation of new silent ischemic lesions may provide positive results in favor of the nCPAP therapy but unfortunately this comparison could not be made because MRI studies at the time of diagnosis were not available in all patients [24,49]. In this respect, it would be also interesting to assess the information provided by neuropsychological performance studies [50,51] and voxel-based morphometry analysis [52].

In relation to cardiovascular deaths, the trend found in our study was towards a lower mortality in the nCPAP group, but early nCPAP treatment in ischemic stroke patients had no effect to reduce the occurrence of new cardiovascular events including ischemic cardiac events, stroke recurrences or mortality. These findings are in some way consistent with data recently reported by Martinez-Garcia and colleagues [34] in a 5-year follow-up study, in which 68 ischemic stroke patients with an AHI ≥ 20 who did not tolerate nCPAP showed increased adjusted risks of mortality compared to patients with an AHI < 20 (hazard ratio 2.69) and to those with AHI ≥ 20 who tolerated nCPAP (hazard ratio 1.58). However, as recognized by the authors, the open-label non-randomized design of the study and the low percentage of adherence to treatment (nearly 30% of patients) are important limitations that should be taken into account. It is likely that patients who did not tolerate nCPAP were those with more severe disease, greater functional impairment or previous stroke and poor prognosis. On the other hand, nCPAP therapy was introduced in the stable phase of stroke, at least 2 months from the onset of symptoms, when the expected functional recovery has already been taken place and data regarding the effect of nCPAP on neurologic outcome cannot be assessed. Nevertheless, another important difference between both studies is the length of follow-up, since the majority of cardiovascular events occurred after 30 months in the referred study, and a follow-up of 24 months in our study might not be prolonged enough (most likely unpowered for secondary outcome of stroke).

On the other hand, our results are similar to those reported in a recent study [53] in which recurrence and vascular death at a mean of 12 months (standard deviation 15 days) was 19.8% in patients with ischemic stroke with polyvascular atherothrombotic disease compared to 12.4% in patients with monovascular atherothrombotic disease. In our study, the rate of cardiovascular events (including cardiac ischemic events, stroke

recurrence and cardiovascular death was 12% (15/126) (12.3% in the nCPAP group, 11.6% in the control group) at 2 years, but almost all events occurred within the first year. However, the mortality in our series was generally low because more severe stroke patients were excluded. In this respect, the percentage of patients with minimal or negligible neurological dysfunction was high (close to 30% in some scales). All of them seemed to be explained in part by the selection related to the inclusion criteria: age < 75 years, first episode of stroke and ischemic stroke, and consciousness to cooperate. Therefore, the non-severe characteristics of stroke patients and the limited follow-up period may account for the low morbidity and mortality observed in the present series. Moreover, the lack of statistical power may be a matter of concern, although differences in mortality between the nCPAP and control groups would be achieved if 100 patients would have been included in each group.

Positive effects of nCPAP in the long-term cannot be excluded. Moreover, early nCPAP treatment in ischemic stroke patients may be beneficial to prevent cardiovascular events on a long-term basis. In the present series of patients, nCPAP was started after a mean (SD) of 4.6 (2.8) days after the onset of stroke following completion of diagnostic studies. If a much earlier nCPAP approach may have lead to a more positive results in favor of the nCPAP group is unknown.

In a pilot study of 12 stroke patients who within 48 h of acute stroke onset underwent sleep studies, nocturnal non-invasive blood pressure studies during CPAP and during spontaneous breathing, and cerebral blood flow velocity measurement in middle cerebral artery with transcranial Doppler during spontaneous breathing and with CPAP, possible harmful hemodynamic effects of CPAP at higher pressures were reported [54]. However, in our study neither systemic hemodynamic values nor cerebral circulatory data were recorded.

The degree of hypoxemia was greater in the nCPAP group than in controls, which in fact might potentiate the positive effect of nCPAP despite acting upon a subset of hypothetically more severe patients. However, in a previous study [10], CT90 was not selected as independent predictor of mortality in the logistic regression analysis in stroke patients with sleep-disordered breathing. A higher CT90 in the nCPAP group may be related to a greater BMI and a higher percentage of alcohol abuse in this group.

In summary, early use of nCPAP in first-ever ischemic stroke patients followed for 24 months seems to accelerate neurological recovery and to delay the appearance of cardiovascular events, although an improvement in survival or in the quality of life of the patients was not shown.

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Table 1. Clinical characteristics of 126 patients with ischemic stroke and moderate-severe obstructive sleep apnea according to randomization to the study groups

	All patients (n = 126)	nCPAP group (n = 57)	Control group (n = 69)	*P* value*
Sex, men/women	89/37	41/16	48/21	NS
Age, years, mean (SD)	64.7 (9.2)	63.7 (9.1)	65.5 (9.1)	NS
Body mass index (BMI), kg/m^2, mean (SD)	29.5 (4.3)	30.2 (4.6)	28.8 (4.0)	NS
Neck circumference, cm, mean (SD)	42.1 (4.0)	41.9 (3.8)	42.3 (4.2)	NS
Snoring (often or always)	113 (89,7)	54 (94.7)	59 (85.5)	NS
Observed apnea at night (often or always)	72 (57.1)	40 (70.2)	32 (46.4)	0.007†
Respiratory data				
Epworth Sleepiness Scale, score, mean (SD)	7.8 (3.8)	8.3 (3.3)	7.3 (4.1)	NS
AHI, mean (SD)	38.4 (13.7)	38.4 (12.6)	38.4 (14.6)	NS
Central sleep apnea	5.5 (8.6)	5.9 (9.4)	5.2 (7.9)	NS
CT90, %, mean (SD)	11.9 (17.0)	15.4 (19.7)	8.9 (13.8)	0.032‡
Vascular risk factors				
Hypertension	76 (61.8)	33 (60)	43 (63.2)	NS
Diabetes mellitus	46 (37.4)	21 (38.2)	25 (36.8)	NS
Atrial fibrillation	8 (6.5%)	2 (3.,6%)	6 (8.8%)	NS
Ischemic heart disease	19 (15.4)	7 (12.7)	12 (17.6)	NS
Chronic obstructive pulmonary disease	8 (6.5%)	3 (5.9%)	5 (7.4%)	NS
Dyslipemia	47 (38.2)	26 (47.3)	21 (30.9)	NS
Smoking	47 (38.2)	25 (45.5)	22 (32.4)	NS
Alcohol abuse	18 (14.6)	12 (21.8)	6 (8.8)	0.043†
Salient clinical features				
Sudden onset	43 (34.7)	19 (33.9)	24 (35.3)	NS
Headache	11 (8.9)	7 (12.5)	4 (5.9)	NS
Motor deficit	69 (55.6)	32 (57.1)	37 (54.4)	NS
Sensory deficit	40 (32.3)	19 (33.9)	21 (30.9)	NS
Speech disturbances	39 (31.5)	14 (25.0)	25 (36.8)	NS
Stroke subtypes				
Atherothrombotic	53 (44.2)	26 (47.3)	27 (41.5)	NS
Cardioembolic	14 (11.7)	6 (10.9)	8 (12.3)	NS
Lacunar	50 (41.7)	21 (38.2)	29 (44.6)	NS
Unusual cause	3 (2.5)	1 (1.8)	2 (3.1)	NS
Undetermined etiology	3 (2.5)	0	3 (4.6)	NS
Topography of infarction (vascular territory)				
Middle cerebral artery	36 (37.1)	16 (36.4)	30 (37.7)	NS
Anterior cerebral artery	0	0	0	
Posterior cerebral artery	3 (3.1)	--	3 (5.6)	
Barthel index, mean (SD)	74.7 (27.3)	75.9 (27.9)	73.6 (27.0)	NS
Canadian scale, mean (SD)	8.2 (1.7)	8.3 (1.6)	8.0 (1.9)	NS
Rankin scale, mean (SD)	2.6 (1.3)	2.3 (1.3)	2.8 (1.3)	NS
Quality of life, SF-36, mean (SD)				
Physical component summary	42.8 (10.4)	42.3 (11.1)	43.1 (7.8)	NS
Mental component summary	47.7 (13.1)	47.1 (13.3)	48.2 (12.9)	NS

Data as number and percentages in parenthesis unless otherwise stated; NS: not significant.

* *P* value differences between the nCPAP group and the control group**.**

† Pearson's (χ2) chi-square test.

‡One-factor ANOVA.

Table 2. Percentage of patients with improvement in the neurological parameters 1 months after stroke

		nCPAP group (n = 57)	Control group (n = 69)	*P* value*	Odds ratio (95% confidence interval)
Barthel index (improvement ≥ 1 point of disability)	All patients	43/52 (82.7%)	45/54 (83.3%)	0.567	--
	Excluding patients with less severe stroke	26/35 (74.3%)	30/39 (76.9%)	0.502	--
Rankin scale (reduction ≥ 1 point/category)	All patients	30/33 (90.9%)	18/32 (56.3%)	0.002	7.78 (1.73–39.84)
	Excluding patients with less severe stroke	21/24 (87.5%)	14/28 (50.0%)	0.004	7.00 (1.47–37.86)
Canadian scale (increase of ≥ 0.5 points)	All patients	45/51 (88.2%)	40/55 (72.7%)	0.038	2.81 (0.91– 9.07
	Excluding patients with less severe stroke	33/39 (84.6%)	28/43 (65.1%)	0.038	2.95 (0.91–9.93)

*P value differences between the nCPAP group and the control group (Pearson's ($\chi 2$) chi-square test).

Table 3. Follow-up data in the groups with and without nCPAP

	With nCPAP (n = 57)	Without nCPAP (n = 69)	*P* value*
Barthel index, mean (SD)			
Baseline	75.9 (27.9)	73.6 (27.0)	NS
3 months	95.0 (13.4)	92.8 (17.8)	NS
12 months	95.3 (10.0)	91.4 (17.8)	NS
24 months	94.3 (10.9)	93.1 (15.8)	NS
Canadian scale, mean (SD)			
Baseline	8.3 (1.6)	8.0 (1.9)	NS
3 months	9.3 (1.0)	9.3 (1.3)	NS
12 months	9.4 (1.2)	9.4 (1.3)	NS
24 months	9.3 (1.3)	9.5 (1.0)	NS
Rankin scale, mean (SD)			
Baseline	2.3 (1.3)	2.8 (1.3)	NS
3 months	1.6 (0.9)	2.0 (1.1)	NS
12 months	1.6 (0.9)	2.1 (1.2)	NS
24 months	1.8 (1.1)	2.2 (1.1)	NS
SF-36, physical component summary			
1 month	42.6 (10.2)	42.3 (11.8)	NS
3 months	44.9 (9.2)	44.8 (11.8)	NS
12 months	46.7 (8.8)	46.5 (11.7)	NS
24 months	45.8 (10.0)	46.0 (9.8)	NS
SF-36, mental component summary			
1 month	43.3 (13.2)	43.7 (14.1)	NS
3 months	46.9 (10.9)	46.3 (14.4)	NS
12 months	49.1 (14.0)	44.6 (12.8)	NS
24 months	47.6 (13.8)	47.8 (12.1)	NS

**P* value differences between the nCPAP group and the control group (one-factor ANOVA); NS: not significant.

Table 4. Outcome: cardiovascular events and mortality

	With nCPAP (n = 57)	Without nCPAP (n = 69)
Cardiovascular events		
Stroke	3	3
Transient ischemic attack	1	
Angina	1	
Myocardial infarction	1	
Other events	1	2
Deaths	2	3
Cardiovascular-related deaths		3
Non-cardiovascular related deaths	2	

Legends

Figure 1. Flow chart of the study population.

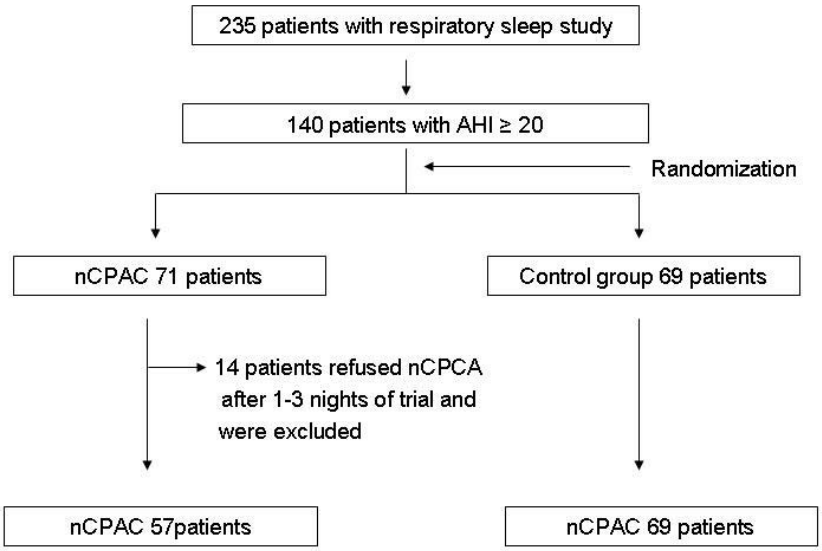
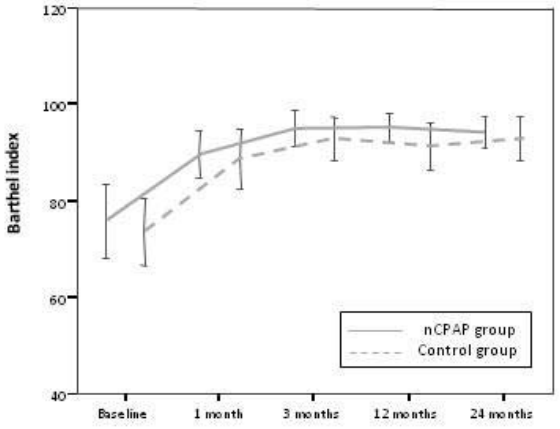
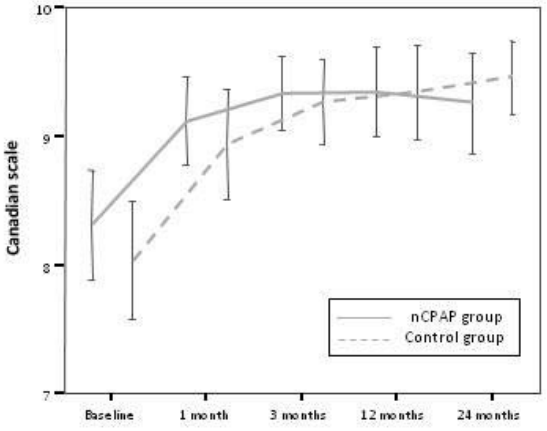


Figure 2. Changes in the mean values of the Barthel index, Canadian scale and Rankin score throughout the study.


Barthel index
120
100
80
60
40
nCPAP group
Control group
Baseline
1 month
3 months
12 months
24 months


Canadian scale
10
9
8
7
nCPAP group
Control group
Baseline
1 month
3 months
12 months
24 months

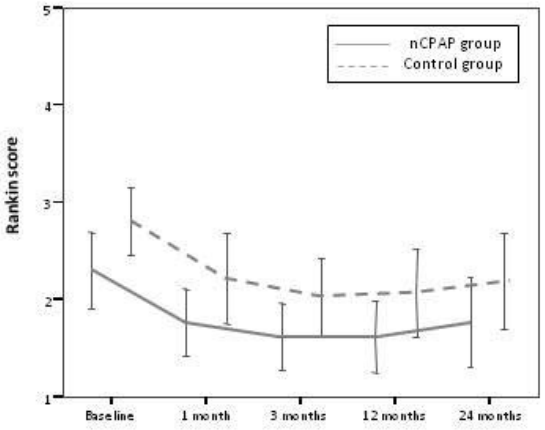

Rankin score
5
4
3
2
1
nCPAP group
Control group
Baseline
1 month
3 months
12 months
24 months

Figure 3. Overall free-cardiovascular event survival in the nCPAP and control groups.