SCIENTIFIC INVESTIGATIONS

Expiratory Positive Airway Pressure for Sleep Apnea after Stroke: A Randomized, Crossover Trial

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Study Objectives: Obstructive sleep apnea (OSA) is common after stroke and predicts poor outcomes. Continuous positive airway pressure (CPAP) treats OSA but is generally poorly tolerated by stroke patients. We assessed whether nasal expiratory positive airway pressure (EPAP), an alternative to CPAP, may be an effective option after acute stroke.

Methods: We conducted a randomized, controlled, two-period crossover study in which each acute ischemic stroke patient received 1 night of EPAP and 1 night without EPAP while OSA was monitored with a validated device, the Watch-PAT 200. Linear repeated-measures analyses were conducted. Sample size calculations indicated that 18 subjects would be required to detect a 10-point or larger average reduction in the apnea-hypopnea index (AHI, the primary outcome), with use of EPAP, with power ≥ 80% and α = 0.05.

Results: Among the 19 subjects who completed the protocol, nasal EPAP treatment was associated with a nonsignificant absolute difference in AHI of −5.73 events/h in the primary analysis (p = 0.183, 95% confidence interval −14.4, 2.97) and a nonsignificant absolute difference in AHI of −5.43 events/h in the subgroup of patients who used nasal EPAP for ≥ 3 h (p = 0.314, 95% confidence interval −16.6, 5.76).

Conclusions: This study suggests that EPAP is not an effective alternative to CPAP in acute stroke patients with OSA. Further work is needed to identify other more effective alternatives.

Clinical Trial Registration: ClinicalTrials.gov, ID: NCT01703663

Keywords: obstructive sleep apnea, positive pressure respiration, stroke

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INTRODUCTION

Obstructive sleep apnea is (OSA) is a serious medical condition that affects the majority of patients with ischemic stroke.[1] Sleep apnea is an independent risk factor for stroke, with increase in risk associated with higher apnea-hypopnea index (AHI).[2] Moreover, sleep apnea is an important predictor of poor functional outcome after stroke.[3,4] Sleep-disordered breathing has been associated with a higher risk of death or dependency 6 months after stroke.[3] Many factors likely underlie this association, including detrimental effects of hypoxia on brain recovery[5] and the effects of poor sleep quality and daytime somnolence on patient participation with rehabilitation.

Although the negative effects of OSA on stroke recovery have been demonstrated, the benefits of OSA treatment have not been definitively tested. The most effective therapy for OSA outside the context of stroke is continuous positive airway pressure (CPAP), but adherence to this therapy historically has been particularly poor in stroke patients.[1,6,7] For example, one 2006 study evaluating nasal CPAP after stroke found generally poor acceptance rates for nasal CPAP initiated during stroke unit hospitalization,[8] with reasons including family/caregiver discomfort with the practical requirements for CPAP use,

BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea (OSA) is widely prevalent after ischemic stroke and is associated with higher mortality and worsened outcomes, but stroke patients as a group may not tolerate conventional continuous positive airway pressure (CPAP). This study was designed to test the effects of nasal expiratory positive airway pressure (EPAP) within this important population.

Study Impact: This study supports the feasibility of diagnostic and clinical interventions for OSA during acute hospitalizations after stroke, but suggests that EPAP is not likely to treat OSA effectively in acute stroke patients intolerant to CPAP. Alternatives to CPAP and EPAP should be identified.

cognitive dysfunction or sundowning, and inability of patients with motor deficits to adjust this equipment. Positional therapy has been studied as a possible substitute for positive pressure treatment of sleep apnea after stroke,[9] but with only moderate improvements in sleep apnea severity. Other alternatives to CPAP have not been studied in this population.

A simpler and possibly more tolerable alternative to CPAP is expiratory positive airway pressure (EPAP), which has been shown to reduce apneas in the general population.[10,11] EPAP is

provided by disposable valves, applied nightly to the nares; the valves provide resistance on expiration but little or no resistance on inspiration. Given the high prevalence of OSA, poor CPAP adherence after stroke, absence of a highly effective alternative approach to treatment of OSA in the poststroke setting, and promising preliminary findings with EPAP therapy in nonstroke patients, we tested whether EPAP use may be tolerable and effective to reduce OSA severity specifically in acute stroke patients.

METHODS

We prospectively recruited alert subjects age 18 y or older who were admitted to the inpatient neurology service at the University of Michigan with an ischemic stroke, including transient ischemic attack with infarct,[12] within the previous 14 days (ClinicalTrials.gov identifier: NCT01703663). The study protocol was approved by the University of Michigan Institutional Review Board. After consent from the patient or surrogate, study subjects were monitored on 2 consecutive nights with the Watch-PAT 200 (Itamar Medical, Israel), an FDA-approved portable diagnostic device consisting of a finger-mounted peripheral arterial tonometry (PAT) probe, a wrist-mounted device, and oxygen saturation monitor, without snoring monitor. The Watch-PAT 200 has been well validated against standard in-laboratory polysomnography.[13–15] The device records PAT, heart rate, oxygen saturation, and actigraphy, which are then analyzed by device software. The PAT detects episodes of upper airway obstruction indirectly through identification of altered sympathetic tone, whereas actigraphy data are used to distinguish sleep versus wakefulness and estimate sleep time. A respiratory event is identified by any of three criteria in an attempt to approximate diagnostic criteria for clinical research[16]: (1) a PAT amplitude reduction with corresponding increase in pulse rate or in wrist activity, (2) a PAT amplitude reduction with a $\geq 3\%$ oxygen desaturation, or (3) a $\geq 4\%$ oxygen desaturation. An AHI is calculated as the number of respiratory events per hour of sleep.

The Watch-PAT was particularly well suited for this research because it does not require a nasal pressure or airflow sensor, which may be ineffective during use of EPAP.[17] Patients were determined to have OSA if they had an AHI ≥ 5 on either the treatment night or the control night. Only data obtained during sleep time, based on Watch-PAT actigraphy data, were included in AHI calculations.

The study intervention consisted of nasal EPAP administered with the Provent device (Ventus Medical, Inc., Manchester, NH, now owned by Theravent, Inc.). Provent consists of two single-use valves (one in each nostril) held in place with an adhesive ring. This intervention was administered following a randomized, controlled, two-period crossover design (AB/BA) in which each patient underwent 1 night of EPAP and 1 night without EPAP, randomized to the order of treatment on a 1:1 basis. Two consecutive nights were used to limit the period effect, as OSA can improve over weeks to months after an acute stroke.

Other than age and presence of acute ischemic stroke, there were no other specific criteria for inclusion into the study population and initiation of the EPAP protocol. Exclusion criteria included contraindications identified by the Provent manufacturer, specifically known severe cardiopulmonary comorbidities such as heart disease, acute respiratory infection, pneumothorax, bullous lung disease, or other chronic respiratory disorders. Patients with medical comorbidities that preclude use of nasal EPAP, including transnasal tubes or current use of mechanical ventilation, CPAP, or supplemental oxygen, were also excluded. Other exclusion criteria included factors that affect accuracy of the WatchPAT, including use of alpha blockers or short acting nitrates, a permanent pacemaker, or sustained nonsinus arrhythmia.

A priori sample size calculations determined that at least 18 subjects were needed to detect a 10-point difference in the AHI with a power $\geq 80\%$, $\alpha = 0.05$, and a two-sided test, based on the assumption that the within-patient standard deviation of AHI (based on night-to-night variability) is 10.[18] The required sample size in crossover trials is typically substantially reduced compared with parallel group trials because between-subject variability is eliminated as subjects serve as their "own control."[19] The primary pre-specified study outcome variable was AHI. Prespecified secondary outcomes included mean and minimum oxygen saturation and an oxygen desaturation index calculated as the number of oxygen desaturations of $\geq 4\%$ per hour of sleep time. Other exploratory outcomes included sleep efficiency (the amount of sleep time divided by the total recording time). The treatment effect of EPAP on AHI, oxygen saturation, and time spent asleep were estimated using a linear repeated-measures model, which accounts for the correlation of repeated measures within the same subject. A treatment-by-period interaction was planned to assess for crossover effect. The treatment-by-period interaction was non-significant and therefore was dropped from all models. Primary analyses were performed using an intention-to-treat analysis, which included, as part of the prespecified analysis plan, all patients who had an AHI ≥ 5 during at least 1 of the 2 nights (either the control night or the intervention night, or on both nights). Sensitivity analyses were conducted for two subgroups: (1) excluding those with AHI ≥ 5 on the intervention night but AHI < 5 on the control night, and (2) excluding those with fewer than 3 h of self-reported use of EPAP. Descriptive statistics were used to assess self-reported measures reported on a questionnaire administered by interview the day after EPAP use.

RESULTS

Forty subjects consented to participate in the study. Twenty did not complete the study protocol because of technical difficulties with the Watch-PAT or hospital discharge before completion of study protocol (**Figure 1**). No subject was excluded due to removal of or intolerance to the EPAP device. Of the 20 subjects who completed the study protocol, one subject had AHI < 5 on both nights and was therefore excluded from analysis. The 19 remaining enrolled subjects were mostly male, in advanced middle age or older, and overweight or obese. Most had hypertension and/or hyperlipidemia, and almost one in four had a

Figure 1—CONSORT flow diagram.
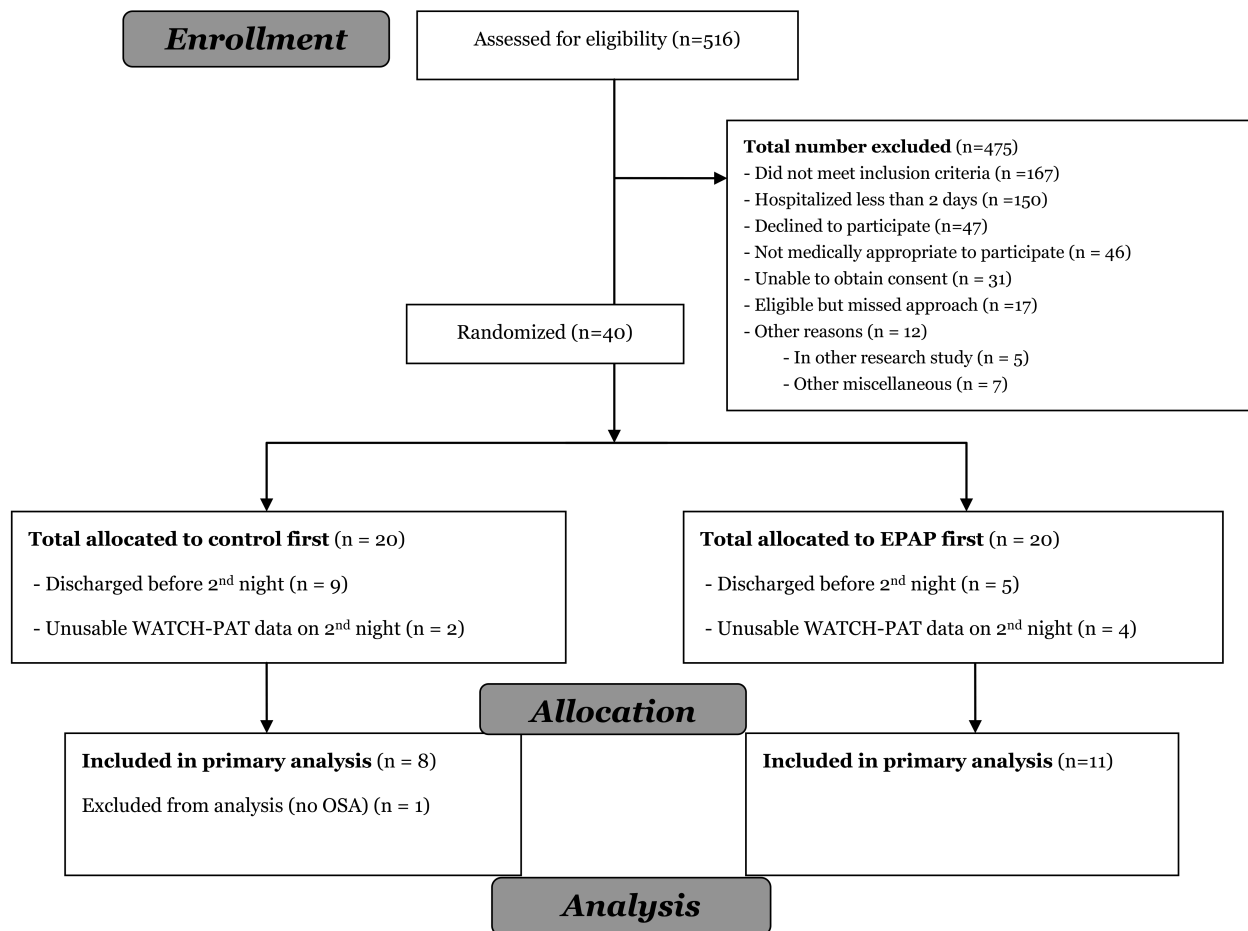
EPAP, expiratory positive airway pressure; OSA, obstructive sleep apnea.

previous diagnosis of OSA. Full baseline demographic and clinical characteristics are summarized in **Table 1**.

Primary, Secondary, and Exploratory Analyses

In the primary analysis, median AHI was 17.1 on the intervention night and 25.2 on the control night. Nasal EPAP treatment was associated with a nonsignificant AHI difference derived from the model of −5.73 (95% confidence interval −14.4, 2.97) in the primary analysis. Similarly, model results did not differ by treatment night for oxygen desaturation, mean oxygen saturation, lowest oxygen saturation, or sleep efficiency (**Table 2**).

Sensitivity Analyses

Sensitivity analysis was performed to exclude one subject whose AHI was ≥ 5 on the treatment night but with AHI < 5 on the control night, with similar results compared to the primary analysis (data not shown). Sensitivity analysis including only subjects who self-reported at least 3 h of EPAP use also showed nonsignificant AHI reductions (**Table 2**).

Self-Reported Measures

In general, the majority of subjects reported good tolerability of the EPAP device, with more than 75% reporting use for

more than 3 h. A significant minority did report some discomfort or difficulty breathing associated with use of this device. Detailed results of subject self-reported subjective sleep quality and tolerability of the EPAP device are included in **Table 3**.

DISCUSSION

This randomized, controlled, 2-night crossover trial of nasal EPAP therapy for OSA suggests that nasal EPAP is tolerable but not adequately effective in acute ischemic stroke patients. Although a small difference in AHI may have been missed, given 80% power to detect an AHI difference of ≥ 9.6 as confirmed by *post hoc* calculations, this study argues against a clinically satisfactory treatment effect of EPAP in acute stroke patients.

One possible explanation for this negative result could be that Provent is less effective in stroke patients than in nonstroke patients, though the clinical or physiological basis for this is not clear. Furthermore, although early studies of nasal EPAP in the general OSA population demonstrated a modest but meaningful reduction in AHI throughout a range of sleep

apnea severity,[10,20] newer evidence suggests that nasal EPAP may be less effective than previously believed.[21] A recent study compared CPAP, nasal EPAP, and placebo in a small group of patients with known moderate to severe OSA and found similar recurrence of OSA in the nasal EPAP and placebo EPAP groups.[21] Nasal EPAP, like conventional CPAP, has also been associated with development of complex apneas and an increased frequency of central apneas during treatment.[22] Existing evidence suggests that in stroke patients obstructive apneas are much more common than central apneas at baseline,[23] but it is possible that the measured AHI during EPAP treatment may have captured some purely central or complex apneas.

Other possible explanations for this negative result include (1) underestimation of treatment effect due to possible inadequate EPAP use, though sensitivity analysis that excluded those with poorer self-reported use showed similar results, and (2) overestimation of treatment effect in prior studies due to inaccurate measurement of AHI.[17] The current study is unique among EPAP trials in that it assessed OSA without introducing possible measurement error from a nasal pressure cannula inserted through the EPAP device.[17]

With respect to tolerability, most patients reported nasal EPAP use for greater than 3 h during the intervention night. Furthermore, sleep efficiency was similar on the EPAP and no EPAP nights, even in those with EPAP use ≥ 3 h per night, which suggests that EPAP use did not substantially interfere with sleep. However, several subjects reported discomfort or subjective breathing difficulty during the night associated with the EPAP device use. Tolerability of nasal EPAP in the acute

Table 1—Patient characteristics.

	All Patients (n = 19)	Patients with ≥ 3 h of EPAP Use (n = 15)
Demographic characteristics		
Male	12 (63)	10 (67)
Age (y)	60 (55, 70)	60 (51, 70)
Patient-reported BMI (kg/m^2)	29.1 (26.6, 33.5)	29.0 (26.6, 41.3)
Medical record BMI (kg/m^2)	28.9 (27.2, 34.3)	28.7 (27.2, 40.1)
NIHSS score	4 (2, 6)	4 (2, 6)
Medical history		
Hypertension	12 (63)	10 (67)
Diabetes	7 (37)	5 (33)
Atrial fibrillation	1 (5)	1 (7)
Hyperlipidemia	16 (84)	13 (87)
Prior stroke	5 (26)	3 (20)
Current smoker	5 (26)	5 (33)
Coronary artery disease	3 (16)	3 (20)
Renal failure	0 (0)	0 (0)
Previous diagnosis of OSA	5 (26)	5 (33)

Values presented as n (%) or median (IQR). BMI, body mass index; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OSA, obstructive sleep apnea.

Table 2—Sleep characteristics: raw data and model results.

	All Subjects (n = 19)*		Subjects with ≥ 3 h of EPAP Use (n = 15)*		All Subjects (n = 19)[†]	Subjects with ≥ 3 h of EPAP Use (n = 15)[†]
	EPAP night	Control night	EPAP night	Control night	EPAP night	EPAP night
AHI (events/h)	17.1 (13.2, 26.5)	25.2 (14.2, 49.6)	19.5 (15.8, 48.3)	25.2 (17.4, 62.9)	−5.73 (−14.4, 2.97)	−5.43 (−16.6, 5.76)
Oxygen desaturation index	9.6 (7.0, 14.7)	15.5 (4.9, 39.6)	10.0 (7.9, 29.0)	17.2 (5.5, 42.2)	−3.39 (−10.7, 3.94)	−3.48 (−12.9, 5.91)
Mean oxygen saturation (%)	92 (91, 94)	92 (91, 93)	92 (91, 93)	92 (90, 93)	−0.21 (−0.74, 0.31)	−0.20 (−0.73, 0.33)
Lowest oxygen saturation (%)	86 (82, 88)	87 (78, 88)	84 (76, 88)	85 (78, 87)	0.58 (−1.52, 2.68)	1.00 (−1.67, 3.67)
Sleep efficiency (%)	74.6 (70.0, 83.3)	79.0 (68.0, 86.7)	75.7 (70.0, 83.3)	74.6 (63.9, 86.7)	−0.4 (−6.87, 6.07)	1.19 (−6.41, 8.79)

*Median (IQR). [†] Model-derived difference (95% CI). AHI, apnea-hypopnea index; CI, confidence intervals; EPAP, expiratory positive airway pressure; IQR, interquartile range.

Table 3—Patient perception of the sleep experience, and subjective tolerability of the provent expiratory positive airway pressure device.

	All Patients (n = 19 except where specified)
Number of hours wearing EPAP (n = 17), mean (SD)	6.8 (3.2)
Ease of falling asleep, mean (SD) [a]	1.2 (1.9)
Ease of staying asleep, mean (SD) [a]	1.2 (2.0)
Difficulty breathing, mean (SD) [b]	1.7 (3.1)
Difficulty of breathing due to EPAP in those who reported difficulty (n = 5), mean (SD) [c]	8.8 (1.3)
Number who removed the EPAP before the end of sleep, n (%)	7 (37)
Number who would wear EPAP at least sometimes if prescribed (n = 18), n (%)	16 (89)
Number who found the EPAP at least somewhat comfortable, n (%)	12 (63)

[a] Scale 0 (extremely easy) to 10 (extremely hard). [b] Scale 0 (no difficulty) to 10 (a lot of difficulty). [c] Scale 0 (not all caused by EPAP) to 10 (entirely caused by EPAP). EPAP, expiratory positive airway pressure; SD, standard deviation.

stroke population may not generalize to the larger population of patients with sleep apnea.

OSA prevalence was very high in this population of acutely hospitalized stroke patients, and the reason for this particularly high prevalence is not clear. Although information concerning specific infarction location and size was not collected, existing observational data do suggest a high frequency of sleep apnea in the stroke population overall,[23] with a prevalence of approximately 84% in stroke patients with brainstem involvement and 59% in patients with other infarction locations.[24] We do not think that this particularly high prevalence can be attributed to other factors relating to the subtype or size of infarct, as other observational studies have not found differences in the prevalence of sleep-disordered breathing based on ischemic stroke subtype,[25] stroke severity, or infarction size.[26]

Limitations of the study include use of the Watch-PAT device, which, although well validated, is not the gold standard measure of OSA and sleep duration, and which required exclusion criteria that diminish the generalizability of results. We also lacked objective measures of EPAP use, though patient self-reported surveys did suggest that most patients were able to use EPAP for at least 3 h during the treatment night. Another limitation is that sleep time and device adherence were measured by actigraphy and patient self-report, respectively, rather than objective monitoring with full polysomnography or direct visualization. This may overestimate sleep duration and device adherence, which may influence our estimates of the effect of EPAP treatment. We note, however, that sensitivity analysis did not show a significant effect on AHI even when limited to patients with high self-reported use. Use of nasal EPAP for only 1 night may also underestimate its medium- or long-term efficacy, as patients were not given several nights of treatment to adjust to the device, as this was not feasible in the context of a crossover design during the acute stroke hospitalization. We did not collect data about long-term efficacy or tolerability of nasal EPAP in the acute stroke population.

CONCLUSIONS

This study supports the feasibility of diagnostic and clinical interventions for OSA during acute hospitalizations after stroke, but suggests that EPAP is not likely to treat OSA effectively in acute stroke patients intolerant to CPAP. Alternatives to CPAP and EPAP should be identified in this important population.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CPAP, continuous positive airway pressure
EPAP, expiratory positive airway pressure
IQR, interquartile range
NIHSS, National Institutes of Health Stroke Scale
OSA, obstructive sleep apnea

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SUBMISSION & CORRESPONDENCE INFORMATION

DISCLOSURE STATEMENT