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Brief Communication

Do apneas and hypopneas best reflect risk for poor outcomes after stroke?

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ABSTRACT

Objective/Background: Sleep apnea (SA) is associated with poor outcomes after stroke. The best sleep apnea-related measure to capture this relationship is currently unknown. This measure or its underlying pathophysiology could serve as a treatment target.
Patients/Methods: Within the population-based Brain Attack Surveillance in Corpus Christi (BASIC) project, the ApneaLink Plus was used to perform sleep apnea tests shortly after ischemic stroke (2010–2015). Functional and cognitive outcomes were measured via in-person interviews 90-days post-stroke. Recurrent stroke was assessed longitudinally through active and passive surveillance procedures. After standardization to allow direct comparisons, adjusted models were built for each ApneaLink Plus measure and each outcome, to assess the effect of 1 standard deviation difference in the measure.
Results: Among 995 subjects, median age was 67 years (interquartile range: 59, 78) and 52% were women. The respiratory event index had the strongest relationship with functional outcome (mean difference = 0.094, 95% confidence interval (CI): 0.040, 0.147). Desaturations ≤85% were associated with worse functional outcome (mean difference = 0.016, 95% CI: 0.002, 0.030), but desaturations ≤ 90% were not. Obstructive apnea index (OAI) showed the strongest association with cognitive outcome (mean difference = −0.079, 95% CI: −0.162, 0.005), but was not significant. Oxygen desaturation index (ODI) showed the strongest association with recurrent ischemic stroke (hazard ratio = 1.338, 95% CI: 1.016, 1.759).
Conclusions: Measurements easily obtained from a commonly used home sleep apnea test predicted outcomes differentially. This suggests the possibility of different SA-associated targets (perhaps using strategies more tolerable than standard treatment) based on the outcome of interest.

Studies of sleep apnea (SA) during acute stroke or subsequent rehabilitation hospitalizations suggest that the majority of such patients have SA, specifically obstructive rather than central sleep apnea [1]. SA is associated with increased dependence after stroke, longer acute rehabilitation stays, poorer functional outcome at both the time of admission and the time of discharge from rehabilitation, and poor longer-term functional outcome [2–5]. We recently showed, within a population-based sample, that SA is associated with functional and cognitive outcome and recurrent stroke [6,7].

The apnea hypopnea index (AHI), a reductive single measure meant to summarize an entire night's polysomnographic (PSG) data, is likely insufficient to characterize SA fully [8]. Other SA measures, such as oxygen desaturations, may be better predictors than AHI of stroke risk [9,10]. These other measures of SA have not been compared as predictors of post-stroke outcomes. Identification of alternative treatment targets aside from AHI may clarify what continuous positive airway pressure (CPAP) titrations should address, or broaden treatment alternatives. To address this identified knowledge gap among

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participants with recent stroke, we compared models that used a variety of potential predictors of stroke outcomes, each derived from a commonly used home sleep apnea test (HSAT).

1. Methods

Data were obtained from the Brain Attack Surveillance in Corpus Christi (BASIC) Project, an ongoing stroke surveillance study that takes place along the gulf coast of Texas. Detailed methods have been published previously [11]. Acute stroke cases are identified through active and passive surveillance among all seven acute care hospitals within Nueces County. Cases are validated, after review of source documentation, by fellowship-trained stroke physicians. Subjects are eligible for enrollment into BASIC if they reside in this county at least six months per year, and have a stroke that was not the result of trauma. Subjects are offered enrollment into a SA substudy if they are identified within 30 days of stroke onset through active surveillance, or within 45 days through passive surveillance. Exclusions from SA testing include pregnancy or current use of oxygen supplementation, positive airway pressure, or mechanical ventilation.

Screening for SA is performed with the well-validated [12] ApneaLink Plus HSAT, applied during or soon after the stroke hospitalization. In comparison to PSG, the manufacturer published a correlation coefficient of 0.94 for the apnea index, 0.85 for the obstructive apnea index (OAI), and 0.94 for the central apnea index (CAI) [13]. This device records airflow (nasal pressure), respiratory effort (chest movement), oxygen saturation, and pulse and is categorized as an Out-of-Center $S_0C_4O_{1X}P_0E_4R_2$ based on the Sleep, Cardiovascular, Oximetry, Position, Effort, and Respiratory (SCOPER) classification [14]. Raw data were reviewed and edited by a registered PSG technologist to eliminate artifact and adjust start/stop time. The ApneaLink software then computed the following variables: respiratory event index (REI: sum of apneas and hypopneas per hour of recording), oxygen desaturation index (ODI), minimum desaturation, desaturations to $\leq$85%, desaturations to $\leq$90%, CAI, OAI, and hypopnea index. Each count variable was calculated per hour of recording. Our hypopnea definition used the 4% threshold, without assessment for arousal, consistent with the recommended definition at the time the study commenced [15]. Detailed definitions of apneas and hypopneas used have been published previously [16].

Two key types of outcomes were assessed at in-person interviews with subjects at 90 days after stroke. Functional outcome was measured by an activities of daily living (ADL) and instrumental activities of daily living (IADL) scale where the total scores ranged from 1 (representing no difficulty with ADLs/ADLSs) to 4 (representing can only do ADLs/IADLs with help). Cognitive outcome was measured by the modified mini-mental state examination (MMMS); scores ranged from 0 to 100 (best score). Covariates were ascertained by medical record review or baseline interview. Recurrent ischemic stroke was assessed using the same surveillance methods described for case ascertainment. Mortality was ascertained based on next-of-kin report and Texas Department of State Health Services records.

Subjects for the current report are limited to those with ischemic stroke (2010–2015). Race/ethnicities other than non-Hispanic white and Mexican American were excluded from the current analysis due to very small numbers. This project is approved by the University of Michigan and local Corpus Christi hospital systems' Institutional Review Boards. Written informed consent is obtained from the subject or legally authorized representative.

1.1. Statistical analysis

Missing data for the ApneaLink and other covariates were imputed (multiple imputation) based on a regression predictive matching algorithm. ApneaLink Plus measures, cognitive, and functional outcome were rescaled to have a mean of 0 and a standard deviation of one such that each calculated beta coefficient is directly comparable and describes the change in outcome for a 1-standard deviation change in the predictor. See Table 1 for the means and standard deviations of the original scales. We considered the absolute value of the estimates from the models to compare the size of the effect irrespective of direction. Correlations among the original ApneaLink Plus measures were examined.

Logistic regression was used to generate inverse probability weights to account for data missing at different stages of participation, using standard methods [17]. Mean differences with 95% confidence intervals (CI) were used for functional and cognitive outcomes, and hazard ratios (HR) were used for ischemic stroke recurrence. Specifically, separate weighted linear regression models were built for the individual ApneaLink Plus measurements and each functional and cognitive outcome, adjusted for potential confounders: age, sex, ethnicity, vascular risk factors (hypertension, diabetes, prior stroke/TIA, coronary artery disease, atrial fibrillation, hypercholesterolemia, current smoking, excessive alcohol), body mass index, prestroke Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), pre-stroke modified Rankin Scale, intravenous tissue plasminogen activator, and initial NIH Stroke Scale. Cause-specific proportional hazards models were used to test the association between each predictor and recurrent stroke, accounting for mortality as a competing risk. Subjects with a history of prior history of stroke/TIA were excluded from these time-to-event analyses.

2. Results

Of the 995 subjects with outcome assessments, 623 had successful ApneaLink studies. Supplementary Table 1 summarizes baseline characteristics, ApneaLink Plus measures, and outcomes for the complete and imputed ($n = 995$) data. The median age was 67 (interquartile range: 59, 78) and about half (52%) were women. Median time from stroke to ApneaLink Plus study was 13 days [IQR = (7, 22)]. Approximately 63% of these subjects had an REI $\geq$10. Correlations among the specific ApneaLink Plus variables are found in the Fig. 1. The most strongly correlated were REI and ODI (0.87, $p < 0.0001$). Of the 715 subjects with no history of stroke/TIA prior to the index event, 55 developed recurrent ischemic strokes. Ninety-eight subjects died without yet having had a stroke recurrence. The median follow-up time was 1.66 years (IQR: 0.69, 3.24).

For the functional outcome measures, the standardized REI had the largest mean difference, followed by OAI, CAI, and ODI (Table 1). Saturation events $\leq$85% were associated with worse functional outcome, but desaturations $\leq$90% were not.

For the cognitive outcome, the OAI had the largest mean difference, followed by the REI and ODI (Table 1). None of these associations with cognitive function reached significance, although both the REI and ODI associations were of borderline significance.

For recurrent ischemic stroke, the ODI had the greatest HR followed by REI (Table 1). Although only ODI was significantly associated with recurrent stroke, both OAI and REI were borderline significant.

3. Discussion

This sizeable, multicenter, prospective, observational study suggests that ODI in comparison to REI has a stronger association with recurrent ischemic stroke. The association is significant for ODI but not for REI. This suggests that ODI could be a better predictor of recurrent ischemic stroke than REI. This study did not identify an HSAT measure more strongly associated than REI

Table 1
Adjusted associations between ApneaLink measures and functional and cognitive outcomes.

Outcome	Predictor[a]	Direction of association	Mean difference (95% CI)	P-Value
ADL/IADL[b] (rescaled by SD = 1.00)	REI	+	0.094 (0.040, 0.147)	0.001
	Min Desat	−	0.057 (0.002, 0.112)	0.041
	Sat ≤85% (per hour)	+	0.016 (0.002, 0.03)	0.026
	Oxygen desat index	+	0.058 (−0.003, 0.118)	0.061
	Sat ≤90% (per hour)	+	0.005 (−0.003, 0.014)	0.236
	Central apnea index	+	0.072 (0.020, 0.125)	0.008
	Obstructive apnea index	+	0.091 (0.032, 0.15)	0.003
	Hypopnea Index	+	0.023 (−0.031, 0.077)	0.405
3MS Score[c] (rescaled by SD = 1.18)	REI	−	0.064 (0.005, 0.133)	0.067
	Min Desat	+	0.036 (0.046, 0.118)	0.375
	Sat ≤85% (per hour)	−	0.01 (0.006, 0.026)	0.218
	Oxygen desat index	−	0.053 (0.025, 0.131)	0.178
	Sat ≤90% (per hour)	−	0.008 (0.006, 0.022)	0.239
	Central apnea index	−	0.042 (0.047, 0.131)	0.339
	Obstructive apnea index	−	0.079 (0.005, 0.162)	0.064
	Hypopnea Index	−	0.006 (0.058, 0.069)	0.861
	Predictor	Direction of association	Hazard ratio (95% CI)	P-value
Recurrence	REI	+	1.297 (0.956, 1.758)	0.094
	Min Desat	−	1.064 (1.240, 1.404)	0.66
	Sat ≤85% (per hour)	+	1.008 (0.932, 1.089)	0.846
	Oxygen desat index	+	1.338 (1.016, 1.759)	0.038
	Sat ≤90% (per hour)	+	1.031 (0.994, 1.071)	0.104
	Central apnea index	+	1.011 (0.749, 1.363)	0.945
	Obstructive apnea index	+	1.261 (0.991, 1.606)	0.059
	Hypopnea Index	+	1.209 (0.892, 1.637)	0.219

REI: respiratory event index; Min desat: minimum desaturation; ODI: oxygen desaturation index; CAI: central apnea index; OAI: obstructive apnea index.
[a] Predictors were standardized to be directly comparable and described as the change in the rescaled outcome to assess a 1 standard deviation difference in the measure. Mean (SD) after standardization: REI: 0.076 (1.03); Min Desat: −0.06 (1.05); Sat ≤85% (per hour): 1.84 (4.73); ODI: 0.05 (1.02); Sat ≤90% (per hour): 3.83 (6.92); CAI: 0.04 (1.03); OAI: 0.12 (1.03); Hypopnea: 0.01 (1.04).
[b] Higher ADL/IADL scores indicate worse function.
[c] Higher MMMS scores indicate better cognitive outcome.

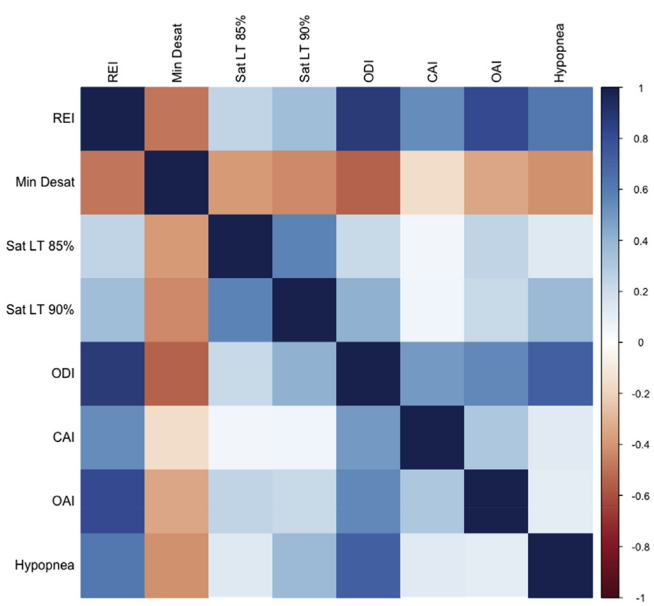

Fig. 1. Correlations among ApneaLink Plus variables. REI: respiratory event index; Min desat: minimum desaturation; Sat LT 85%: saturation ≤85%; Sat LT 90%: saturation ≤90%; ODI: oxygen desaturation index; CAI: central apnea index; OAI: obstructive apnea index; hypopnea: hypopnea index.

with post-stroke functional or cognitive outcome. Notably, despite the low frequency of central apneic events, not only OAI but also CAI predicted post-stroke functional outcome. Moreover, oxygen desaturations to ≤85% were associated with functional outcome but desaturations to ≤90% were not. This suggests the possibility of a threshold effect. In our data, hypopneas were not associated with worse outcomes. Reasons for this are unclear, but hypopneas are known to contribute less to arousals and desaturations than apneas [18]. One possibility is that reliability of scoring for apneas exceeds that for hypopneas. However, the lack of association between hypopneas and functional and cognitive outcome, and the possible desaturation threshold effect, have potential implications for prognostication and CPAP titration aims in stroke patients. Furthermore, this study points to the possibility of different SA-associated targets — perhaps using strategies more tolerable than CPAP just after stroke – based on the outcome of interest.

Longer and deeper desaturations, in comparison to shorter, shallower desaturations even when more frequent, may result in more severe health consequences. Novel markers of apnea and desaturation severity and duration have been shown to be associated with mortality when AHI was not [19,20]. Additional studies should be conducted to determine whether novel measurements of desaturation length and depth, not currently available from typical HSAT software output, provide better or additional value compared with REI, in stroke outcome prediction.

Limitations of this study include the use of an HSAT rather than laboratory-based PSG. However, the device used has been validated in many studies and application of HSATs has been validated among ischemic stroke patients [21]. Strengths of the study include the use of imputation and inverse probability weighting methods to minimize selection bias, and a large, population-based, and well-characterized sample of stroke patients.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.006.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.05.006.

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