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Research letter

Hypoxic burden and heart-rate variability predict stroke incidence in sleep apnoea

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"take home" message: Indices of sleep apnoea-related hypoxic burden and heart rate variability derived from full-night polysomnography might be useful for identifying sleep apnoea patients at risk for stroke.

Keywords: Obstructive sleep apnoea; hypoxic burden, heart rate variability, stroke

Obstructive sleep apnoea (OSA) is increasingly recognized as a risk factor for stroke [1]. However, the incidence of stroke in patients investigated for OSA has been assessed in a limited number of studies reporting conflicting results on the association between the apnoea-hypopnea index (AHI) and stroke incidence [1–3]. As OSA is a very heterogeneous condition, the identification of subgroups of patients at high risk for stroke would be clinically desirable, in order to implement preventive actions [1]. Population-based studies have demonstrated that the sleep apnoea specific hypoxic burden (SASHB), an easily derived signal from polysomnography (PSG), predicts cardiovascular mortality and incident heart failure [4, 5]. A recent study has demonstrated that night-time heart rate variability (HRV) might play an important role in the association between OSA and the cerebral small vessel disease, which is responsible for a substantial proportion of strokes [6]. Whether physiological markers of SASHB and HRV might be useful in clinical setting for identifying those patients with OSA at risk for stroke remains to be determined. Within a large multicentre clinic-based cohort of patients investigated for OSA, we hypothesized that PSG-derived indices of SASHB and HRV could predict stroke incidence.

The study was conducted on the *Pays de la Loire Sleep Cohort*, linked with data from the French administrative health care database (SNDS) (see ref [7] for details on the *Pays de la Loire Sleep Cohort* and the process linking it with the SNDS). We included stroke-free patients with available SNDS data investigated by PSG (CID102L8DTM, CIDELEC, Sainte-Gemmes-sur-Loire, France) for OSA between May 15, 2007 and December 31, 2017. Respiratory events were scored manually using

recommended criteria [8]. As previously described, the SASHB was defined as the total area under the respiratory event-related desaturation curve [4]. Using standard recommendations [9], HRV was computed on 5 minute segments of continuous non-overlapping PSG-derived ECG without ectopy or artefact. Time domain HRV measurements included the standard deviation for the mean value of all normal-to-normal R-R intervals (SDNN) and the root mean square of successive differences in normal-to-normal R-R intervals (RMSSD). Frequency-domain measurements included the normalized low frequency (LF, from 0.04 to 0.15Hz) and high frequency power (HF, from 0.15 to 0.4Hz). The LF to HF ratio (LF/HF) estimated the sympathetic/parasympathetic tone.

The study endpoint was the first episode of stroke at any time between the PSG recording date and the end of December 2018. The first occurrence of stroke was identified from the national hospital discharge database (PMSI) and defined as the entry date of the first hospitalization with a discharge diagnosis G45, G46, I60-I64, or I69 [10]. The accuracy of PMSI-based algorithm for stroke has been previously demonstrated with a positive predictive value at 90% [10]. As all physicians routinely contribute to PMSI data collection with annual quality control of coding, the accuracy increases with time [11].

Cox proportional hazard models were used to evaluate the association of stroke incidence with natural log transformed indices of OSA severity and HRV. Missing values were imputed using a multiple imputation method (MI procedure from SAS) [7]. Associations were considered statistically significant for a p value <0.05. All statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC).

The study population consisted of 3,597 patients (median [interquartile range, IQR] age: 58 [48-67] years), predominantly male (63%), obese or overweight (median [IQR] body-mass index [BMI] = 28 [25-32] kg/m^2), frequently presenting cardiovascular and metabolic comorbidities (hypertension, 28.6%; diabetes, 10.4%; cardiac diseases, 8.7%), 85.4% of whom had mild-to-severe OSA (median [IQR] AHI = 20 [8-35] events/h). During follow-up, 1,159 patients were positive airway pressure (PAP)

adherent (mean daily PAP use≥4 h). After a median follow-up of 5.9 [3.5-8.4] years, 83 patients had been diagnosed with a stroke including 70 ischemic (29 transient ischemic attack, TIA) and 13 haemorrhagic strokes (stroke incidence density rate = 3.9 per 1,000 person-years). Cox proportional hazard models (Table 1) demonstrated an association between natural log transformed indices of OSA severity and stroke incidence (Model 1), which remained significant after adjusting for confounding risk factors (Model 2) for SASHB and the percentage of sleep time with oxygen saturation <90% (T90) (p=0.02 for both). Among natural log transformed indices of HRV, stroke incidence was negatively associated with LF and LF/HF ratio (p=0.01 and 0.008 respectively) and positively associated with HF (p=0.01) after adjusting for confounders (Model 2). The magnitude of the associations was unchanged after adjusting for PAP adherence (Model 3) and controlling for a competing risk of death (not shown).

When the analysis was restricted to 70 ischemic cerebrovascular events, stroke incidence remained significantly associated with natural log transformed SASHB (adjusted hazard ratio, HR [95% confidence interval]: 1.30 [1.05-1.61]; p=0.02) and LF/HF ratio (adjusted HR: 0.66 [0.47-0.93]; p=0.02) in the fully adjusted model (Model 3). After exclusion of 29 TIA from the analysis, stroke incidence remained significantly associated with natural log transformed LF/HF ratio (adjusted HR: 0.60 [0.41-0.90]; p=0.01) but not with SASHB (adjusted HR: 1.17 [0.92-0.1.48]; p=0.2).

Adding interaction terms in the analyses showed no significant interaction of gender and PAP adherence in the relationship between natural log transformed PSG-derived indices and stroke incidence. However, stroke incidence was more strongly associated with SASHB and HF among non-obese subjects compared with those with obesity. The association of stroke incidence with SASHB and LF/HF was also stronger in patients aged ≥ 60 years compared with those aged <60 years (all p values for interactions <0.05).

In a large multicentre, clinic-based cohort, we demonstrated an association of stroke incidence with PSG-derived indices of OSA-related hypoxaemia and HRV. Patients with higher SASHB and lower

sympathetic/parasympathetic tone (LF/HF ratio) were at higher risk of stroke after adjusting for confounding risk factors and PAP adherence.

A strong association between untreated OSA and incident strokes (n=17 events) have been previously reported in women [2]. Conversely, Kendzerska et al. [3] reported that stroke in OSA was not associated with AHI. In the present study, we found no relationship between stroke incidence and common metrics of OSA severity excepted for T90 which characterizes not only OSA-related intermittent hypoxaemia, but also persistent hypoxaemia, such as that due to obesity hypoventilation or heart failure. Conversely, we demonstrated a dose-response relationship between stroke incidence and SASHB. Altogether, our findings and those from recent reports [4, 5] suggest that SASHB might predicts stroke and cardiovascular morbidity more consistently than AHI, ODI and T90.

Previous studies have demonstrated a relationship between HRV and stroke [12]. In subjects with OSA, the sympathetic activation that occurs toward the end of obstructive events is accompanied by vagally mediated bradycardia due to activation of the diving reflex [13]. In older men with OSA, sleep-related reduced sympathetic/parasympathetic tone is associated with a higher risk of atrial fibrillation [14], which has been consistently associated with stroke risk. In the present study, a one-unit increase in natural log transformed LF/HF ratio was associated with a 44% decrease in stroke risk, suggesting a contribution of low sympathetic/parasympathetic tone to stroke occurrence.

The strength of the current study includes a multicentre design, the adjustment for multiple stroke risk factors, and the assessment of different OSA severity and HRV indices. Our study also has some limitations. Its observational design does not allow any conclusions to be drawn regarding the causal pathway of the associations. Potential unmeasured confounding factors cannot be excluded. The use of a composite outcome combining different types of cerebrovascular events is also a potential limitation. We acknowledge that our study did not have sufficient statistical power to examine the association of OSA severity and HRV indices with the different stroke subtypes. All patients were

investigated by in-laboratory overnight PSG using the same device. Further studies are required to evaluate the reproducibility of PSG-derived indices of SASHB and HRV. Furthermore, the high prevalence of OSA has led to an increasing use of simplified home sleep apnoea testing, with no ECG signal [15]. Whether oximetry-derived indices of pulse rate variability could provide an accurate estimation of HRV and predict stroke incidence should be also evaluated.

In conclusion, within a large clinic-based cohort of patients with suspected OSA, we demonstrated an association of SASHB and nigh-time sympathetic/parasympathetic tone with stroke risk. PSG-derived indices of hypoxic burden and heart rate variability may provide an opportunity to allow for stroke risk stratification in patients with OSA.

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Table 1: Cox proportional hazard models assessing the association of indices of obstructive sleep apnoea (OSA) severity and heart rate variability (HRV) with stroke incidence.

	Hazard ratio [95% confidence interval]		
	Model 1	Model 2	Model 3
Indices of OSA severity			
ln AHI	1.45 [1.15-1.84] †	1.18 [0.93-1.50]	1.20 [0.93-1.55]
ln SASHB	1.46 [1.24-1.72] ‡	1.25 [1.04-1.51] *	1.28 [1.05-1.57] *
ln MAI	1.44 [1.01-2.05] *	1.20 [0.86-1.68]	1.21 [0.86-1.71]
ln 3%ODI	1.30 [1.09-1.55] †	1.13 [0.95-1.33]	1.13 [0.95-1.35]
ln T90	1.11 [1.06-1.16] ‡	1.06 [1.01-1.12] *	1.06 [1.01-1.12] *
Indices of HRV			
ln SDNN	0.97 [0.59- 1.61]	1.19 [0.73- 1.95]	1.23 [0.75- 2.04]
ln RMSSD	1.36 [0.93- 1.98]	1.43 [0.99- 2.07]	1.43 [0.99- 2.07]
ln LF	0.36 [0.21-0.64] ‡	0.47 [0.26- 0.85] *	0.47[0.26-0.86] *
ln HF	3.35 [1.48- 7.61] †	2.78 [1.25- 6.17] *	2.77 [1.25- 6.16] *
ln LF/HF ratio	0.59 [0.43-0.81] †	0.66 [0.48-0.90] †	0.66 [0.48-0.90] †

Abbreviations: ln, natural log transformed; AHI, apnoea-hypopnea index; MAI, micro-arousal index; ODI, oxygen desaturation index; T90, percentage of sleep time with oxygen saturation <90%; SDNN, standard deviation for the mean of value of all normal-to-normal R-R intervals; RMSSD, root mean square of successive differences in normal-to-normal R-R intervals; LF, normalized low frequency power; HF, normalized high frequency power.

Model 1: unadjusted

Model 2: adjusted for age, gender, body mass index, alcohol intake, smoking status, diabetes, hypertension, history of cardiac disease and study site.

Model 3: Model 2 + adjusted for positive airway pressure adherence

* $p<0.05$; † $p<0.01$; ‡ $p<0.001$