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Sleep Apnea and Asymptomatic Carotid Stenosis
A Complex Interaction

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BACKGROUND: Carotid arteriosclerosis and sleep apnea are considered as independent risk factors for stroke. Whether sleep apnea mediates severity of carotid stenosis remains unclear. Sleep apnea comprises two pathophysiologic conditions: OSA and central sleep apnea (CSA). Although OSA results from upper airway occlusion, CSA reflects enhanced ventilatory drive mainly due to carotid chemoreceptor dysfunction.

METHODS: Ninety-six patients with asymptomatic extracranial carotid stenosis of ≥ 50% underwent polysomnography to (1) determine prevalence and severity of sleep apnea for different degrees of carotid stenosis and (2) analyze associations between OSA and CSA, carotid stenosis severity, and other arteriosclerotic risk factors.

RESULTS: Sleep apnea was present in 68.8% of patients with carotid stenosis. Prevalence and severity of sleep apnea increased with degree of stenosis ($P \leq .05$) because of a rise in CSA ($P \leq .01$) but not in OSA. Sleep apnea (OR, 3.8; $P \leq .03$) and arterial hypertension (OR, 4.1; $P \leq .05$) were associated with stenosis severity, whereas diabetes, smoking, dyslipidemia, BMI, age, and sex were not. Stenosis severity was related to CSA ($P \leq .06$) but not to OSA. In addition, CSA but not OSA showed a strong association with arterial hypertension (OR, 12.5; $P \leq .02$) and diabetes (OR, 4.5; $P \leq .04$).

CONCLUSIONS: Sleep apnea is highly prevalent in asymptomatic carotid stenosis. Further, it is associated with arteriosclerotic disease severity as well as presence of hypertension and diabetes. This vascular risk constellation seems to be more strongly connected with CSA than with OSA, possibly attributable to carotid chemoreceptor dysfunction. Because sleep apnea is well treatable, screening should be embedded in stroke prevention strategies.

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ABBREVIATIONS: cAHI = central apnea-hypopnea index; CSA = central sleep apnea; oAHI = obstructive apnea-hypopnea index; PPV = positive pressure ventilation; tAHI = total apnea-hypopnea index

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Arteriosclerotic carotid stenosis and sleep apnea are considered to be independent risk factors of stroke.[1-3] Whether severity of carotid arteriosclerosis is also mediated by sleep apnea remains unclear. In coronary artery disease, sleep apnea is found in > 50% of patients and is related to severity of coronary arteriosclerosis.[4,5] Further, it is associated with early arteriosclerotic changes and endothelial dysfunction in the carotid artery.[6] However, both the prevalence of sleep apnea and its association with stenosis severity in patients with asymptomatic carotid artery stenosis are unknown.

According to its pathophysiology, sleep apnea can be subdivided into OSA and central sleep apnea (CSA). OSA is the consequence of partial or complete upper airway occlusion and has been recognized as a coronary and peripheral arteriosclerotic risk factor.[4,5] CSA reflects enhanced ventilatory drive primarily due to peripheral (carotid) chemoreceptor dysfunction and has been demonstrated in patients with asymptomatic extracranial carotid stenosis.[7,8] The interference of carotid arteriosclerosis and chemoreceptor function results in autonomic dysregulation.[7,8] Autonomic dysregulation facilitates coronary and peripheral arteriosclerosis and is strongly associated with cardiovascular and cerebrovascular morbidity and mortality.[9-13]

In this study, we prospectively determined the prevalence and severity of sleep apnea syndrome and its subtypes in patients with asymptomatic extracranial carotid stenosis. We hypothesized that sleep apnea is a risk factor for carotid stenosis severity because (1) OSA is a risk factor for the development and severity of peripheral and coronary arteriosclerosis and (2) CSA reflects chemoreceptor dysfunction, which also facilitates arteriosclerosis.

Materials and Methods

The study was approved by the Jena University Hospital Ethics Committee (N° 2020-05/07). Written informed consent was obtained from all study participants.

Patients

Between 2007 and 2012, outpatients diagnosed with asymptomatic carotid stenosis (≥ 50% luminal narrowing) and referred to the Jena University Hospital for continuative cerebrovascular risk assessment were recruited for the study. Baseline study examinations included extracranial and transcranial color-coded duplex sonography, echocardiography, and polysomnography, as well as blood gas analysis and an MRI scan of the brain, in addition to cervical and intracranial magnetic resonance angiography. Degree of carotid stenosis was assessed by extracranial sonography (Siemens Corporation) using established ultrasound criteria.[14]

According to our hypothesis, sleep apnea should be present more frequently in patients with severe carotid stenosis than in patients with mild/moderate stenosis. Consequently, patients with a stenosis of < 70% of the extracranial internal carotid artery (left or right) were assigned to a mild/moderate stenosis group and those with stenosis ≥ 70% to a severe stenosis group. If bilateral stenosis was present, the higher value (left or right) was considered for analysis. Cardiovascular comorbidities (coronary arterial disease, myocardial infarction, peripheral vascular disease), medication, and arteriosclerotic risk factors including diabetes mellitus, dyslipidemia, smoking, and alcohol intake based on medical records and/or patient information were documented for each patient.

Exclusion Criteria: Patients with symptomatic extracranial carotid stenosis (ie, neurologic deficits within the last 6 months, detection of ischemic brain lesion on diffusion weighted and T2 MRI scan sequences or both), history of stroke, intracranial carotid stenosis, or carotid dissection were excluded. Presence of concomitant diseases that have a major impact on sleep apnea including heart failure (New York Heart Association functional classification of heart failure III-IV or left ventricular ejection fraction < 50% in echocardiography), global respiratory failure (Po_2 < 60 mm Hg and Pco_2 ≥ 45 mm Hg in blood gas analysis), renal failure requiring dialysis, and neurodegenerative diseases were also considered as exclusion criteria.

Sleep Apnea Detection

Standard polysomnography (SOMNOmedics GmbH) was performed in all patients within 1 week of admission. Scoring for sleep stages and respiratory events was undertaken by experienced personnel according to the relevant guidelines.[15,16]

Central apnea was defined by an absence of tidal volume and thoracoabdominal breathing motion for at least 10 s, central hypopnea with a ≥ 30% reduction in both tidal volume and thoracoabdominal movement for at least 10 s with proportionate thoracoabdominal in-phase movements followed by oxyhemoglobin desaturation of ≥ 4% and/or an EEG arousal without snoring together with increased inspiratory flattening of the nasal pressure flow signal, or thoracoabdominal out-of-phase movements.[15,16] Obstructive apnea/hypopnea was defined by either the absence (apnea) or a ≥ 30% reduction of tidal volume excursion (hypopnea) and maintained thoracoabdominal breathing efforts for at least 10 s followed by ≥ 4% oxyhemoglobin desaturation and/or an EEG arousal. Mixed apneas were classified as obstructive events because of their unknown origin. Total apnea-hypopnea index (tAHI), obstructive apnea-hypopnea index (oAHI), and central apnea-hypopnea index (cAHI) were calculated and represent the number of events per hour. The presence of sleep apnea syndrome was defined by a tAHI of ≥ 10. OSA subtype or CSA subtype was classified if tAHI was ≥ 10, and the relative number of obstructive or central events was at least 50%.[15,16]

Statistical Analysis

Data were analyzed using SPSS Statistics 20 (IBM). Prevalence of sleep apnea and its subtypes (OSA and CSA) together with the corresponding Wilson 95% CIs were estimated for all patients with carotid stenosis and also separately for patients with mild to moderate and severe stenosis.

Patient characteristics including demographics, concomitant diseases, arteriosclerotic risk factors, and respiratory sleep parameters (tAHI, oAHI, cAHI) with severity of stenosis as categorical factor were analyzed for all patients using Student *t* test for continuous variables (means, SDs, and 95% CIs) and χ^2 test or Fisher exact test for categorical variables (frequencies and Wilson 95% CIs). Multivariate logistic and linear regression analyses were performed to assess predictive values of (1) sleep apnea in general, and (2) OSA and CSA for stenosis severity under consideration of age, sex, BMI, and other established