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Sleep Apnea and Asymptomatic Carotid Stenosis
A Complex Interaction

Jens Ehrhardt, MSc; Matthias Schwab, MD; Sigrid Finn, MD; Albrecht Guenther, MD; Torsten Schultze, MSc; Otto W. Witte, MD; and Sven Rupprecht, MD

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

AFFILIATIONS: From the Hans Berger Department of Neurology, Jena University Hospital, Jena, Germany.

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CORRESPONDENCE TO: Sven Rupprecht, MD, Hans Berger Department of Neurology, Jena University Hospital, Erlanger Allee 101, D-07740 Jena, Germany; e-mail: Sven.Rupprecht@med.uni-jena.de

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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

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arteriosclerotic risk factors (eg, diabetes mellitus, dyslipidemia, smoking, arterial hypertension) as covariates. In addition, predictive value of sleep apnea subtypes (OSA, CSA) for arterial hypertension was assessed by multivariate logistic regression analyses under consideration of age, sex, BMI, dyslipidemia, smoking, and diabetes mellitus as covariates. Similarly, predictive value of apnea subtypes for diabetes mellitus was analyzed under consideration of age, sex, and BMI as covariates.

Results

Patients

Ninety-six patients aged between 39 and 86 years (mean age, 65.9 ± 10.0 years) with asymptomatic extracranial stenosis were recruited for the study (64 men and 32 women). Of these, 21 patients had mild/moderate and 75 patients severe carotid stenosis. Patients with severe stenosis were older than those with mild/moderate stenosis (67.2 ± 9.0 years vs 61.4 ± 11.9 years, $P \leq .05$). Frequency of arterial hypertension ($P \leq .01$) and diabetes mellitus ($P \leq .05$) was higher in the severe stenosis group compared with mild/moderate stenosis group (Fig 1, e-Table 1). Both groups did not differ in BMI and left ventricular ejection fraction in the presence of coronary artery disease, myocardial infarction, peripheral vascular disease, dyslipidemia, smoking status, and alcohol intake (Fig 1, e-Table 1).

Prevalence and Severity of Sleep Apnea

Overall prevalence of sleep apnea was 68.8% (Fig 1). OSA was present in 41.7% and CSA in 27.1% of patients. Prevalence of sleep apnea was higher in patients with severe stenosis (76.0%) compared with those with mild/moderate carotid stenosis (28.5%, $P \leq .01$) (Fig 1, e-Table 1). Sleep apnea severity (tAHI) was higher in the severe stenosis group compared with the mild/moderate stenosis group ($P \leq .009$). Increase in sleep apnea severity was based on an increase in cAHI ($P \leq .001$) but not in oAHI, reflecting an augmentation of CSA and not of OSA in patients with severe compared with mild/moderate carotid stenosis (Fig 2, e-Table 1).

Association Between Sleep Apnea and Carotid Stenosis Severity

Sleep apnea (OR, 3.81; $P \leq .03$) and arterial hypertension (OR, 4.11; $P \leq .05$) were independent predictors of carotid stenosis severity in the multivariate logistic regression analysis (overall percentage of correct prediction, 78.1%; $P \leq .16$) (Table 1). Smoking, BMI, dyslipidemia, age, sex, and diabetes had no predictive value. The degree of CSA ($P \leq .06$) but not OSA (indicated by cAHI and oAHI) tended to be associated with stenosis

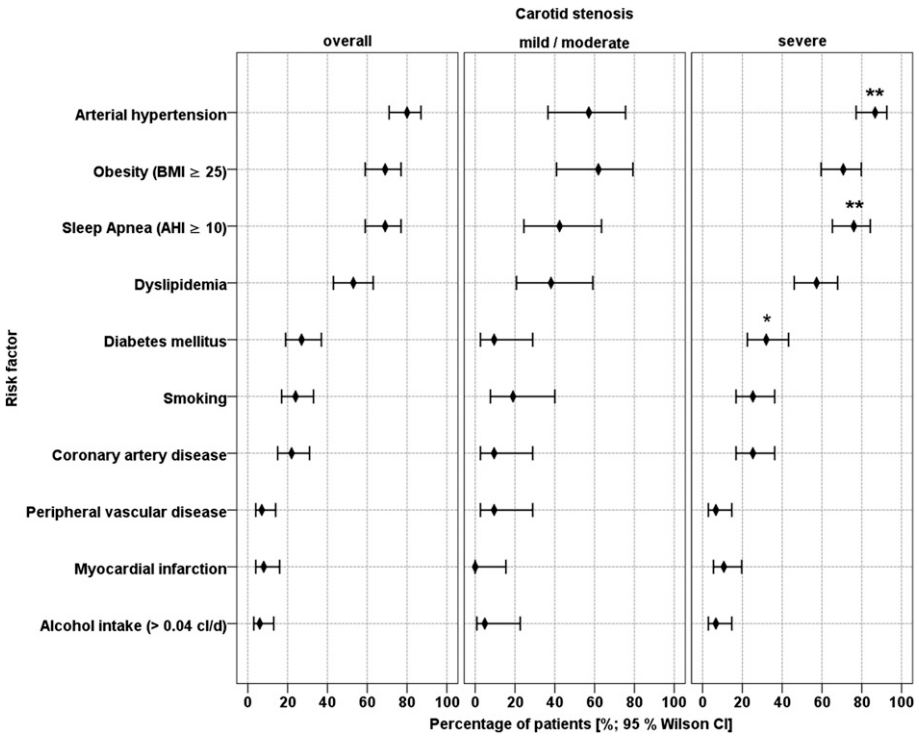


Figure 1 – *Prevalence of sleep apnea, cardiovascular risk factors, and concomitant vascular diseases in patients with asymptomatic extracranial carotid stenosis in relation to the severity of stenosis.* *P ≤ *.05*; **P ≤ *.01* frequency in patients with mild/moderate compared with severe stenosis. *AHI = apnea-hypopnea index.*

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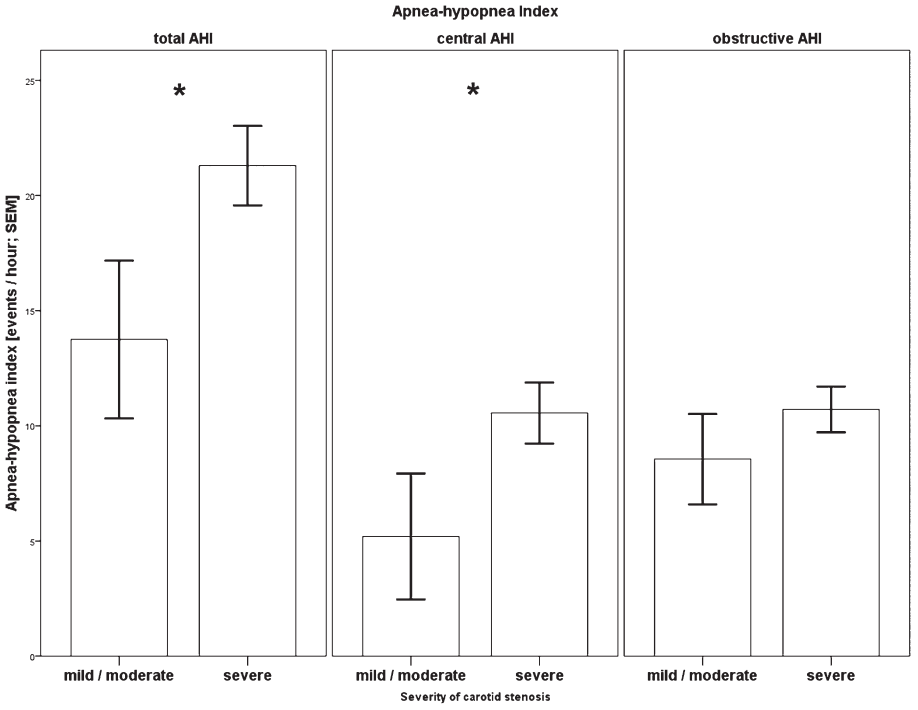


Figure 2 – *Severity of sleep apnea and its subtypes (central sleep apnea, OSA) in patients with mild/moderate stenosis compared with severe stenosis. Sleep apnea severity is reflected by the AHI. Values are given as mean ± SEM, *P ≤ .05. See Figure 1 legend for expansion of abbreviation.*

severity in the multivariate linear regression analysis (R^2, 0.20; $P \leq .02$) (Table 2).

Association Between Sleep Apnea and Classic Arteriosclerotic Risk Factors

Univariate analysis showed an association of stenosis severity to sleep apnea, arterial hypertension ($P \leq .031$) and diabetes mellitus ($P \leq .031$) but not with dyslipidemia. The multivariate logistic regression model assessing the predictive value of OSA and CSA for arterial hypertension under consideration of diabetes mellitus, dyslipidemia, BMI, smoking, and sex as covariates was rejected by means of the goodness-of-fit test (Hosmer-Lemeshow test, $P \leq .001$). Limiting the regression model to CSA and OSA as variables revealed CSA (OR, 2.5; $P \leq .021$) but not OSA as an independent predictor for arterial hypertension (overall percentage of correct

TABLE 1] Adjusted Associations Between Sleep Apnea, Demographics, Classic Arteriosclerotic Risk Factors, and Carotid Stenosis Severity

	Carotid Stenosis Severity, Mild/Moderate vs Severe Stenosis		
Risk Factor	OR	95% CI	*P* Value
Hypertension	4.11	1.02-16.47	.05
Sleep apnea	3.81	1.12-13.10	.03
Diabetes mellitus	2.61	0.46-14.98	.28
Sex	2.26	0.59-8.58	.23
Smoking	1.06	0.25-4.44	.94
Age	1.03	0.97-1.09	.32
Dyslipidemia	0.98	0.29-3.31	.98
BMI	0.92	0.80-1.05	.20
Constant term	0.29	…	.68

TABLE 2] Adjusted Associations Between the Severity of Sleep Apnea Subtypes (CSA, OSA) Demographics, Classic Arteriosclerotic Risk Factors, and Carotid Stenosis Severity

	Degree of Carotid Stenosis, %			
Risk Factor	B	95% CI	β	*P* Value
Hypertension	12.83	3.66 to 22.01	0.31	.01
Sex	4.30	−3.16 to 11.76	0.12	.26
Diabetes mellitus	1.07	−6.85 to 9.00	0.03	.79
CSA (cAHI)	0.27	−0.01 to 0.55	0.19	.06
Age	0.26	−0.09 to 0.61	0.16	.14
OSA (oAHI)	0.23	−0.16 to 0.62	0.12	.25
BMI	−0.25	−1.07 to 0.57	−0.06	.55
Dyslipidemia	−0.13	−7.08 to 6.81	0	.97
Smoking	−2.40	−10.36 to 5.55	−0.06	.55
Constant term	48.44	12.79 to 84.09	…	.01

Severity of CSA and OSA is reflected by the cAHI and oAHI, respectively. Results are presented by the regression coefficient (B) and the standardized regression coefficient (β). cAHI = central apnea-hypopnea index; CSA = central sleep apnea; oAHI = obstructive apnea-hypopnea index.

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prediction, 69.9%; $P \leq .99$) (Table 3). CSA (OR, 4.48; $P \leq .042$) but not OSA, BMI, age, and sex independently predicted presence of diabetes mellitus in the multivariate logistic regression analysis (overall percentage of correct prediction, 74.0%; $P \leq .75$) (Table 4).

Discussion

Sleep apnea is highly prevalent in patients with asymptomatic extracranial carotid stenosis and associated with arteriosclerotic carotid disease severity. Effects of sleep apnea on stenosis severity are primarily linked to CSA but not to OSA. Moreover, CSA but not OSA is associated with presence of arterial hypertension and diabetes mellitus in patients with asymptomatic carotid stenosis.

To our knowledge, this is the first prospective study examining the prevalence of sleep apnea and its association with stenosis severity and other arteriosclerotic risk factors in patients with asymptomatic carotid stenosis. Previous studies focused either on apnea or on early carotid arteriosclerosis when thromboembolic cerebrovascular risk is not yet relevant[6] or else on post stroke patients in whom prevalence and severity of sleep apnea may, in turn, substantially be influenced by the stroke.[1,17-19]

Sleep apnea may contribute directly and indirectly to carotid arteriosclerosis severity. Direct effects are due to the repetitive cessation of breathing in OSA and CSA, resulting in intermittent hypoxia and sympathetic overactivity[20,21] and, thus, eliciting direct proatherogenic effects.[22,23] Indirectly, sleep apnea promotes exacerbation of other arteriosclerotic risk factors such as hypertension, insulin resistance, diabetes, and dyslipidemia.[24-27] Whereas these associations are confirmed for OSA,[24-27] longitudinal studies examining effects of CSA on arteriosclerotic disease and arteriosclerotic risk factors are lacking. In our study, CSA but not OSA was associated with carotid disease severity as well as arterial hypertension and diabetes mellitus. These observations are of course limited by our cross-sectional study design (ie, they do not prove any cause-effect relationship).

TABLE 3] Adjusted Associations Between Sleep Apnea Subtypes (CSA, OSA) and Arterial Hypertension

	Presence of Arterial Hypertension		
Sleep Apnea Subtype	OR	95% CI	*P* Value
CSA	12.50	1.47-106.02	.02
OSA	2.00	0.68-5.92	.21
Constant term	2.00	...	.07

See Table 2 legend for expansion of abbreviations.

TABLE 4] Adjusted Associations Between Sleep Apnea Subtypes (CSA, OSA) and Diabetes Mellitus

	Presence of Diabetes Mellitus		
Risk Factor	OR	95% CI	*P* Value
CSA	4.48	1.05-19.04	.04
BMI	1.10	0.97-1.25	.12
Age	1.05	0.99-1.11	.09
Sex	0.73	0.21-2.53	.62
OSA	0.53	0.40-5.91	.53
Constant term	0.001	...	.03

See Table 2 legend for expansion of abbreviations.

However, the conclusions of our findings are underpinned by population-based longitudinal studies which have shown that CSA rather than OSA predicts stroke incidence and mortality in the normal elderly.[3,28]

CSA can be considered as a ventilatory surrogate marker of peripheral chemoreceptor dysfunction through which an increase in CSA severity reflects increased chemoreceptor activity and vice versa.[29] The assessment of peripheral chemoreceptor activity by means of CSA scoring is a noninvasive and safe alternative to traditional approaches such as estimation of the transient hypoxic ventilatory response, which may represent a potential cerebrovascular risk for patients with carotid stenosis.[13,30] Because CSA is not exclusively associated with carotid stenosis, patients with concomitant diseases predisposing to CSA were excluded from the study.

Because we excluded patients with high probability for CSA due to other reasons, CSA in our cohort may be considered as a functional consequence of the carotid stenosis.[8,12] Even though our observational data do not allow us to address the underlying mechanisms of CSA in carotid stenosis, there are several facts supporting a potential link between CSA and carotid stenosis-mediated chemoreceptor dysfunction. Feeding arteries of carotid chemoreceptors originate directly from the carotid sinus,[31] which is the predilection site of carotid arteriosclerosis.[32] Severe structural damage of carotid bodies and luminal narrowing of feeding arteries are prominent histopathologic features in patients with carotid stenosis.[7,33] Therefore, carotid stenosis gives rise to an impaired blood supply to the carotid bodies. The resulting ischemia and hypoxia of the carotid bodies[34] as the major stimulants of carotid chemoreceptors, in turn, enhance the ventilatory drive.[35,36] Prolonged ischemia and hypoxia intensify chemoreceptor activity, increase peripheral chemoreflex sensitivity, and lead to ventilatory

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instability.[36,37] The latter typically emerges during sleep when ventilation is primarily under homoeostatic control and is reflected in CSA.[36] Severity of CSA directly correlates with peripheral chemoreflex sensitivity.[38-40] An increase in peripheral chemoreflex sensitivity results in sympathetic overactivity, higher BP, and insulin resistance. It also predicts morbidity and mortality for heart and renal failure, coronary artery disease, myocardial infarction, and critical illness.[9,13,41]

Although OSA has been considered to be a major cause of drug-resistant hypertension,[42] CSA rather than OSA was associated with the presence of arterial hypertension in the current carotid stenosis cohort. Because increased peripheral chemoreflex sensitivity is primarily involved in the pathogenesis of essential hypertension,[41] stenosis-mediated chemoreceptor dysfunction reflected by CSA also seems to facilitate hypertension in patients with carotid stenosis. In turn, it has been shown that carotid body denervation and carotid body resection prevent development of hypertension in different animal models[43,44] and in humans with sleep apnea.[45] Taken together, stenosis-mediated carotid chemoreceptor dysfunction results in CSA, which is accompanied by repetitive hypoxia. In turn, hypoxia is a potent mediator of arteriosclerosis. Therefore, carotid arteriosclerosis facilitates carotid chemoreceptor dysfunction and vice versa in a self-perpetuating manner.[3,12,28]

Symptomatic treatment of CSA reduces morbidity and mortality in heart failure in which CSA is highly prevalent and predicts clinical outcome.[46] The most effective therapy for OSA and CSA comprises different forms of nocturnal positive-pressure ventilation (PPV),[46,47] which reduce cardiovascular and cerebrovascular risk primarily in patients with OSA.[47] In OSA, PPV has been found to prevent progression of arteriosclerosis, to improve endothelial dysfunction,[48] and to reverse early arteriosclerotic changes indicated by carotid intima-media thickening.[40] Because these protective effects on arteriosclerotic disease have predominantly been shown in OSA, it remains unclear if PPV has comparable effects in CSA. It would also be of interest whether causative carotid revascularization (ie, removal of the arteriosclerotic plaque), has a beneficial effect on stenosis-mediated chemoreceptor dysfunction and CSA as its phenotypical expression.

Conclusions

Sleep apnea is highly prevalent in asymptomatic extracranial carotid stenosis and associated with arteriosclerotic disease severity. Because it is well treatable, sleep apnea screening should be embedded in stroke prevention strategies.

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Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

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