Sleep apnea in carotid stenosis

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Abstract

OBJECTIVES. Sleep apnea is associated with advanced atherosclerosis. This study was focused on sleep breathing in patients with hemodynamically significant carotid stenosis, currently free from clinical symptoms.

DESIGN AND SETTINGS. 17 patients with carotid artery stenosis of 70% and more in the absence of actual neurological symptoms indicated for non-acute endarterectomy, and 17 age- and sex-matched controls were examined using sleep polygraphy. 12 patients had a follow-up sleep polygraphy a month after the surgery.

RESULTS. The criteria of obstructive sleep apnea (OSA) were met by 4 patients prior to operation, by 2 patients after the operation, and by 2 control subjects. The pre-surgery apnea/hypopnea index (AHI) was 14 (±SD=17.0), post-surgery 8.3 (±9.0) and in the controls 6.7(±6.7). The pre-surgery oxygen desaturation index was 20.1 (±17.7), post-surgery 15.0 (±12.0) and in the controls 11.6 (±6.1). A comparison between the pre-surgery results seen in the patients and in controls after adjustment for BMI revealed no significant difference. The only significant difference between the pre-surgery and post-surgery values was found in the AHI (P=0.045).

CONCLUSION: According to this study there exists an association between carotid stenosis and OSA, however this association is explainable by a higher BMI. The study also found a tendency toward OSA alleviation in response to endarterectomy.

INTRODUCTION

Extracranial stenosis of the carotid arteries is a frequent cause of stroke. The clinical manifestation of carotid stenosis could be transient ischemic attack (TIA) or stroke, although the vast majority of carotid stenosis is asymptomatic. Asymptomatic carotid stenosis affects some 25% of adults, and its incidence is growing with age (Prati *et al,* 1992). The Asymptomatic Carotid Atherosclerosis Study and the more recent Asymptomatic Carotid Surgery Trial have shown net benefit for carotid endarterectomy in neurologically asymptomatic patients with high-grade carotid stenosis (70% or worse) in those under the age of 75 (Halliday *et al,* 2004).

A number of studies offer convincing evidence of an increased risk of ischemic stroke in sleep apnea (Munoz *et al,* 2006, Arzt *et al,* 2005, Yaggi *et al,* 2005). Sleep apnea is also associated with the

ORIGINAL ARTICLE

Abbreviations and units
OSA – obstructive sleep apnea
AHI – apnea/hypopnea index
SD – standard deviation
BMI – Body Mass Index (kg/m^2)
TIA – transient ischemic attack
CI – confidential interval
NYHA – New York Heart Association
ODI – oxygen desaturation index

metabolic syndrome and, thereby, also with accelerated atherogenesis (Parish *et al,* 2007, Lam and Ip 2007) as proven by repeatedly found greater intima-media thickness of the carotid artery in sleep apnea patients (Nachtmann *et al,* 2003, Minoguchi *et al,* 2005, Szaboova *et al,* 2007, Saletu *et al,* 2006, Wattanakit *et al,* 2008, Kaynak *et al,* 2003).

To our knowledge, the relationship between carotid artery stenosis and sleep breathing is dealt with in only three studies, all devoted to stroke survivors. In the first study 22% of 68 patients two months after ischemic stroke or TIA were found to have carotid stenosis – and of these, 80% had an apnea-hypopnea index (AHI – number of apneas and hypopneas per hour) > 30 (Galiano *et al,* 2005). In another study obstructive sleep apnea (OSA) with AHI>20 was found to be associated independently of extracerebral stenosis with an odds ratio of 2.0 (95% CI 1.0–4.1) (Nachtmann *et al,* 2003). In the third study the authors found atherosclerotic lesions to be more prevalent in patients with OSA than in patients without (Dziewas *et al,* 2007).

The purpose of our study was to ascertain the rate of occurrence of sleep apnea in patients with significant though actually clinically silent extracranial carotid stenosis, to compare it with age- and sex-matched controls, and to evaluate changes of their sleep respiration at a month after endarterectomy.

MATERIALS AND METHODS

A specific set of strict criteria for enrollment and exclusion to this study (see below) was applied to all consecutive patients recommended for endarterectomy at the Vascular Surgery Department of Na Homolce Hospital in Prague.

The criteria for enrollment were as follows: recommendation for non-acute endarterectomy for hemodynamically important (70% or worse) unilateral carotid stenosis. This condition was diagnosed with ultrasonography and/or arteriography either in connection with acute neurological symptomatology of vascular etiology (TIA or stroke with complete recovery; Rankin scale 0–1) or in patients who had never had any neurological complaints in their history and whose carotid stenosis was found during comprehensive clinical examination performed for some other reason (e.g., carotid murmur, ischemic disease of the lower extremities, coronary disease).

The criteria for exclusion were as follows: Pathological findings found during neurological examination (incl. cognitive impairment). Severe cardiac insufficiency (NYHA ≥I), infection of upper airways, nasal obstruction, chronic obstructive pulmonary disease, psychiatric disease including anxiety, pain, scoliosis, Bechterev disease, acromegaly, hypothyroidism (also in the past), insufficiently compensated hypertension, benzodiazepine, myorelaxant and antipsychotic drug intake, suspected low compliance with the examination, overall unfavorable health status and lack of interest in participation.

Before the initial and then the follow-up examinations, all the patients were in a stabilized state of health good enough to be examined with nocturnal polygraphy. A total of 17 patients were examined (11 men, 6 women). A checkup polygraphy at one month after endarterectomy was performed in 12 of them (8 men, 4 women). The rest either would not agree to post-surgery polygraphy and one woman was not re-examined for a change in her overall condition due to intracerebral hemorrhage.

Medical history was taken and neurological examination performed by an experienced neurologist (ZŠ), who had also chosen the patients for the study according to the criteria for enrollment and exclusion. BMI (kg/m^2) and neck circumference were measured, and visual oropharyngeal clinical evaluation was rated according to the Mallampati scale (Mallampati *et al,* 1985).

Endarterectomy was performed in general or local anesthesia using standard surgical procedure at the surgeon's discretion (Beneš 2008).

Polygraphy (respiratory flow measured by thermistors in front of the nose and the mouth, chest and abdominal respiratory movements, oxygen saturation, respiratory noises and leg movements, body position) was performed before endarterectomy and 4 weeks after the surgery. Polygraphy was recorderd in a hospital setting between 11.00 p.m. and 6.00 a.m. (in controls at their home or in an old people's home). Only the period indicated as sleep by the patient was analyzed. The results of polygraphy were visually analyzed by one of us (KŠ). Apnea was understood to mean air flow arrest for ten seconds and more, hypopnea – as respiratory amplitude drop by 50% and more accompanied by decreased hemoglobin oxygen saturation. The following parametres were established: the apnea/hypopnea index – AHI (number of apneas and hypopneas per hour), oxygen desaturation index – ODI (number of saturation drops by 3% and more per hour), mean oxygen saturation, time below 90% – the proportion of the time when oxygen saturation was below 90%, and mean heart rate.

The same tests for respiration in sleep were performed in age- and sex-matched volunteers. These controls were examined in their own homes or in an old people's home in Prague. The volunteers received a small remuneration for their participation in the study.

Table I. Patients participating in the study.

Patient	Sex	Age	Neck circumference (cm)	Mallampatti score	BMI	comorbidity	Surgery site	Neurological history	Post surgery polygraphy
1	F	53	39	3	29	HT, DM, smoker	R	TIA	
2	M	62	45	3	32	HT,DM, CAD, smoker	R	TIA	
3	M	70	43	4	2	HT, DM, CAD	L	asymptomatic	X
4	F	81	36	2	24	HT, CAD,HLP	R	TIA	X
5	M	57	45	4	33	HT, DM, CAD treated by bypass, CS, former smoker	R	TIA	X
6	M	55	43	4	27	HT,HLP, former smoker	R	asymptomatic	X
7	F	65	33	3	24	HLP	L	asymptomatic	X
8	F	73	42	4	31	DM, CAD	R	TIA	X
9	M	53	41	2	24	smoker	R	TIA	X
10	M	81	38	3	26	HY, DM, CAD, HLP	R	stroke	
11	F	55	34	4	25	HY, smoker, gastritis	L	asymptomatic	
12	M	72	40	4	24	HY, CAD treated by bypass, HLP, former smoker	R	stroke	X
13	M	62	44	4	29	HY, HLP, smoker	L	asymptomatic	
14	M	77	45	4	33	former smoker	L	TIA	X
15	M	68	41	4	26	HY, CAD, HLP	R	stroke	X
16	M	88	38	3	24	CAD, CS	R	asymptomatic	X
17	F	79	39	4	32	HY, HLP	L	asymptomatic	X
Mean		67.7	40.4	3.5	27.8				
SD		11.1	3.7	0.7	3.5				

F – female, M – male, BMI – body mass index, HT – hypertension, DM – diabetes, CAD – coronary artery disease, HLP – hyperlipoproteinemia, CS – cardiostimulation, R – right, L – left, SD – standard deviation,

Neither the patients nor the controls had any changes made in their regular therapy. Prior to the night registration 3 patients took zolpidem (in two cases 10 mg, and in one patient 5 mg), one patient used bisulepin 2 mg (an antiallergic agent with no known effect on breathing). None of the control group took any hypnotics.

Since, because of their nature, the parameters of sleep apnea are not distributed normally, the results were compared using non-parametric tests (Sign test for paired comparisons of repeated measurements, Man-Whitney test for patients-controls comparisons, and Spearmann's correlation analysis). The patients and controls were compared using ANCOVA, when controlling for covariates, but since the distribution of the residuals was normal, the input prerequisites for this method were not compromised.

The study was approved by the local ethics committee. The patients and controls alike were informed and gave their written informed consent to participation in this study.

RESULTS

The information on the patients, including the relevant comorbidities, is given in Table I. The neck circumference in men was 42.1 (±2.7) cm, in women 37.2 (±3.4) cm. BMI in men was 27.9 (±3.5), in women 27.6 (±3.6). The control subjects' neck circumference was 39.3 (SD=±2.9) cm; in male controls 40.8 (±1.6) cm, in female controls – 36.5 (±2.8) cm. Body mass index (BMI) in the controls was 24.4 (±2.3), that of men – 24.8 (±1.6), that of women 23.5 (±3.0). The BMI of the controls was significantly lower than that of the patients (p=0.002). Found in the control group were four cases of well treated hypertension, one case of diabetes mellitus, while one control subject was taking maintenance medication for a history of signs of depression. The criterion for obesity (BMI≥30) was met by 5 patients and none in the control group.

Stenosis was present on the right side in 11 patients, on the left side in 6 patients. 7 patients had a history of TIA, 3 patients – stroke with full recovery, and 7 were neurologically asymptomatic. The surgery was without complications in all of the patients, and their

Table II. Polygraphy results (mean ±SD)

	Patients		Controls n=17
	Presurgery n=17	Postsurgery n=11	
AHI	14.0 (±17.0)	8.3 (±9.0)	6.7 (±6.7) *
ODI	20.1 (±17.7)	15.0 (±12.0)	11.6 (±6.1)
Mean saturation (%)	93.4 (±2.0)	92.6 (±2.8)	94.8 (±1.2)
time<90%	9.5 (±18.1)	13.5 (±20.9)	1.9 (±3.9)
HR	58 (±6.4)	62.0 (±3.7)	59.0 (±9.0)
AHI≥15 (pts.#)	4 (23.5%)	2 (16.7%)	2 (11.8%)

SD – standard deviation, AHI – apnea/hypopnea index, ODI – oxygen desaturation index, HR, heart rate, vs. – versus, pts.# – number of patients, * – Controls versus presurgery patients P=0.045 (Sign test)

neurological condition at a month after the operation remained unaltered with the exception of one female patient who suffered intracerebral hemorrhage on post-operative day 7. This patient had had no sleep breathing follow-up revision.

The results of polygraphy are summed up in Table II. Practically all sleep respiration abnormalities were obstructive sleep apneas or hypopneas. Central apnea pattern was rarely present in two patients preoperatively, both with a high AHI (52 and 60 respectively). In both cases the diagnostic criteria of central apnea were not met. As none of the patients reported any typical clinical symptoms of sleep apnea, the value of AHI≥15 was adopted as the limit for OSA (American Academy of Sleep Medicine 2005), and found to be exceeded by 4 patients preoperatively (23.5%) and by two controls (11.8%). After endarterectomy, the criteria for OSA were met by two patients (16.7%). The mean and basal saturations were lower in patients then controls (p=0.02 and p=0.03 respectively, Man-Whitney test). After correction according to BMI (ANCOVA), there are no significant patients – controls differences in the sleep time parameters of respiration under study. A comparison of the results of polygraphy before and after endarterectomy shows a slightly lower postoperative AHI (p= 0.045, Sign test).

The differences in AHI before and after surgery correlates with the neck circumference, with the BMI and with the Mallampati score, while the difference in mean oxygen saturation (%) before and after surgery correlates with the neck circumference (p<0.005, R>0.77, Spearman correlation).

DISCUSSION

The finding of a high occurrence of apneas and hypopneas among subjects suffering from carotid stenosis is in agreement with our hypothesis that sleep apnea is prevalent in patients suffering from asymptomatic carotid stenosis. This comes as no particular surprise considering the OSA association with the metabolic syndrome. As follows from the night breathing parameters, sleep apnea occurs more frequently in patients with asymptomatic carotid stenosis than in control subjects. Since the patients were more obese than the control subjects, the adjustment of the results for BMI annulled the significance of the differences. OSA, as found among the carotid stenosis patients, is noted for obviously the same important triggering factor as among the general population, i.e. – obesity. This is corroborated by the correlation between the time below 90%. The pathophysiological role of obesity was frequently neglected by authors of post-stroke cases series (Galiano *et al,* 2005, Nachtmann *et al,* 2003, Dziewas *et al,* 2007). The relationship between carotid plaque and sleep disordered breathing was not recently found in a large number of subjects in Sleep Heart Health Study and the authors emphasized the influence of other cardiovascular disease risk factors (Wattanakit *et al,* 2008).

The presence of a higher BMI in patients with asymptomatic carotid stenosis than in the controls tallies with the idea of accelerated atherogenesis in the metabolic syndrome, which includes obesity (Lam and Ip 2007). This is also consistent with cardiovascular and metabolic comorbidity in the patients despite the fact that serious comorbidity was at variance with the criteria for inclusion and that most of the patients planned for endarterectomy were not enrolled in the study. However, comorbidity could only be compared with the controls for two main reasons: a) the groups were too small and not representative, and b) all information about the control group came from the controls themselves.

The share of the persons meeting the criteria for OSA does exceed the results of prevalence studies, though owing to the non-significant difference from the controls, and owing to the small size of the study population, this finding can hardly be overestimated. Another point to be taken into account is that ischemic stroke results in sleep disordered breathing not only because of advanced atherosclerotic changes in brain-supplying arteries but also due to prothrombotic state

(Dikmenoğlu *et al,* 2006, von Kanel *et al,* 2006), a more frequent occurrence of cardiac arrhythmias and, naturally, also due to a higher occurrence of hypertension (Dopp *et al,* 2007).

The improvement seen in some of the indicators of respiration in sleep at the follow-up polygraphy one month after endarterectomy has no unambiguous explanation. While decreased brain perfusion can set off apnea, in this particular study we have no evidence of reduced brain perfusion in our patients examined before endarterectomy. True, all of them had hemodynamically significant carotid stenosis, but, at the time of examination, this stenosis revealed no clinical signs of impaired brain perfusion. Besides, no such reduction is even theoretically presumed because the risk of stenosis rests in laminary blood flow impairment and in an increased tendency toward thrombogenesis. The impairment (or surgical manipulation) of the carotid artery wall can theoretically influence two structures important to the circulation and respiration: the carotid body and the carotid sinus. The carotid body is thought to function primarily as a respiratory chemoreceptor, reflexively stimulating ventilation in response to arterial hypoxemia or acidosis. Destruction or denervation of the carotid bodies bilaterally results in a virtually complete loss of ventilatory response to hypoxia in the dog (Dejours 1963). The carotid-sinus baroreceptors alter not only the heart rate and peripheral vascular resistance but also myocardial performance in response to changes in carotid arterial pressure (Bevegard and Shepard 1966). Endarterectomy can affect the carotid body as well as the carotid sinus or, more precisely their innervation and vascular supply, but unilateral endarterectomy had little effect on hypoxic responses, and only bilateral endarterectomy abolished them (Wade *et al,* 1970). The carotid body is involved in sleep respiration control and also in the pathophysiology of sleep apnea. Endarterectomy may lead to a change including better perfusion of the glomus caroticum.

The signs of positive post-endarterectomy development of sleep apnea cannot be attributed to post-stroke exaggerated sleep apnea which keeps improving for a number of weeks after stroke anyway (Parra *et al,* 2000).

Nor is there any simple explanation for the marked tendency toward improved respiratory parameters in sleep in patients with typical disposition symptoms of OSA – high BMI (obesity), neck circumference (suggesting an androgenic type of obesity) and a high Mallampati score (a sign of oropharyngeal narrowing) – as these parameters remained unaltered between the two examinations. Conceivably, rather intensive sleep disordered breathing (enhanced by the just mentioned disposition factors) may well show some improvement under the impact of a non-specific intervention in sleep respiration control.

As follows from the results of our study, there exists an association between carotid stenosis without neurological signs at the time of examination and OSA. However, to go by the study, this connection is explainable by a higher BMI in our patients. In some of them OSA subsided in response to endarterectomy, a fact speculatively attributable to the local surgerical action on the glomus caroticum and carotid body. The above correlations will require a study of a larger cohort of patients.

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