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TRIOLOGICAL SOCIETY CANDIDATE THESIS

Snoring and Carotid Artery Disease: A New Risk Factor Emerges

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Objectives/Hypothesis: Previous studies have identified a relationship between snoring, carotid intima media thickening, and the presence of atherosclerosis. This study examines the correlation between snoring and carotid artery disease through use of duplex ultrasound identifying greater than 50% internal carotid artery stenosis.

Study Design: Prospective cohort study.

Methods: Patients presenting to three academic vascular laboratories for carotid duplex examination completed the following surveys: demographic information, assessment of risk factors for carotid stenosis, assessment of history of obstructive sleep apnea, or continuous positive airway pressure use and Snoring Outcomes Survey. Patients were categorized into 2 groups based on the presence or absence of carotid disease. Data were analyzed by univariate contingency tables and logistic regression analysis.

Results: Five hundred one patients completed the survey, of whom 243/501 (49%) had evidence of carotid occlusive disease. On univariate analysis, smoking, hypertension, heart disease, hypercholesterolemia, diabetes, and stroke all correlated with greater than 50% carotid stenosis. Multivariate analysis indicated that snorers were significantly more likely to have carotid disease. Three hundred twenty-seven participants were thought to have primary snoring. On univariate analysis, snorers were found to be significantly more likely to have carotid disease. After adjustment for covariates, snoring was not significant for carotid disease. However, multivariate analysis showed snorers to be significantly more likely to have bilateral carotid disease.

Conclusions: This study shows a potential relationship between snoring and bilateral carotid artery stenosis greater than 50%; snorers have risk of carotid stenosis twice that of nonsnorers. Further investigation is warranted to better elucidate this relationship.

Key Words: Snoring, carotid artery disease, carotid duplex study, obstructive sleep apnea.

Level of Evidence: 2b

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INTRODUCTION

Primary snoring, defined as snoring in the absence of apneic events, traditionally has been thought of as a social nuisance without significant medical consequence. Recent research, however, has begun to show that snoring may adversely affect health.[1] In a study of snorers and nonsnorers with only mild, nonhypoxic obstructive sleep apnea (OSA) syndrome, in which patients underwent polysomnography with quantification of snoring, heavy snoring was significantly associated with carotid atherosclerosis but not with femoral atherosclerosis.[1] A previous study showed a relationship between primary snoring and intima-media thickening of the carotid artery.[2] Patients who identified themselves as snoring all of the time or most of the time in the past 4 weeks were found to have increased intima-media thickening along several points of the carotid artery. Specifically, a comparison of eight points along the carotid arteries (four on the right and four on the left) showed increased intima-media thickening on carotid duplex in snorers compared to nonsnorers.

Intima-media thickness is measured by the combined thicknesses of the endothelial cell monolayer that comprises the tunica intima and the layers of smooth muscle cells composing the tunica media. The traditional risk factors of smoking, hyperlipidemia, and diabetes are known to accelerate thickening of the intima media.[3–5] It is widely accepted that intima-media thickening can predispose an individual to cardiovascular events.[6] A proposed mechanism for the process relates to the anatomic proximity of the carotid arteries to the pharynx. The vibratory effects of the pharynx have been linked to endothelial damage in rabbits.[7] The vibration may act to affect the endothelial tight cell junctions.[8] Given the known relationship between endothelial damage and the development of carotid atherosclerosis, this finding acts to bolster the possibility of snoring acting as a predisposing factor.

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Although the relationship between early carotid vascular disease and snoring has strengthened, efforts are being directed at examining the effects of snoring on clinically significant vascular disease. The most widely accepted, noninvasive measure of carotid occlusive disease is the carotid artery duplex ultrasound. Though a causal relationship is difficult to prove, this multicenter study used carotid duplex ultrasonography to assess the relationship between primary snoring and carotid occlusive disease. Specifically, we aimed to evaluate whether snoring may be associated with clinically significant carotid artery disease independent of the traditional risk factors for carotid artery disease.

MATERIALS AND METHODS

Patients presenting to three academic institutions' vascular laboratories were asked to participate in the study. Institutional review board approval was obtained at all participating centers. Patients who agreed to participate completed an extended questionnaire encompassing a variety of information including demographics, identification of known risk factors of carotid artery disease (smoking, hypertension, heart disease, hypercholesterolemia, diabetes, and stroke), history of OSA or continuous positive airway pressure (CPAP) use, and the Snore Outcomes Survey, which is a validated tool to assess snoring habits.[9,10] Participants were enrolled over the time period of February 2015 to March 2016.

Patients then underwent standard carotid duplex evaluation with measurements of peak systolic velocity and end diastolic velocity at the common carotid artery (CCA) and internal carotid artery, bilaterally. Based on the carotid consensus statement, peak systolic velocity greater than 125 cm/sec is correlated with greater than 50% stenosis.[10] The finding of 50% stenosis is generally regarded as a cutoff whereby surgical intervention, such as carotid endarterectomy, is recommended to patients.[10] Patients were designated to have carotid disease with a CCA peak systolic velocity greater than 125 cm/sec in either carotid artery or a history of a carotid artery procedure (stent or endarterectomy) on either side.

Snoring status was defined based on the Snore Outcomes Survey. This validated questionnaire assesses the severity of snoring. Any participant who answered question 1 of the Snore Outcomes Survey with "all the time" or "most of the time," question 7 with "yes," question 8 with "extremely loud" or "very loud," and question 9 with "most of the time" or "all the time" were classified as snorers. Self-reported use of a CPAP device or history of OSA was used to identify patients with OSA. This allowed for the identification of patients with presumed primary snoring (i.e., nonapneic snoring). Those patients with primary snoring were then compared based on the presence or absence of carotid artery disease using a linear logistic regression analysis. Multivariate analysis was also performed to account for the traditional risk factors for carotid artery disease, which include the following: smoking, hypertension, heart disease, hypercholesterolemia, diabetes, and stroke.

Carotid Artery Duplex Ultrasound

Images of bright mode and color Doppler ultrasound were acquired with a high-resolution, linear, 8 MHz, broadband transducer. Bright-mode images of the left and right internal carotid artery and CCA were visualized in transverse and longitudinal views. Measurements of the carotid arteries were performed at four points on each side: point 1, proximal internal carotid artery (10 mm distal to the flow divider); point 2, carotid bulb (at the flow divider); point 3, distal CCA (10 mm proximal to the flow divider); and point 4, the proximal CCA (20 mm proximal to the flow divider).[11] Ultrasound measurements were analyzed by vascular technologists and by an experienced, interpreting physician, who were blinded to the snoring status of the subjects. The procedures were performed in an outpatient vascular laboratory.

TABLE I.
Demographic and Risk Factor Data for All Participants

Variable	All Subjects	Subjects With Primary Snoring
Average age, yr	68.8	69
Female	22.6% (113/500)	29.1 (95/327)
Male	77.4% (387/500)	70.1% (232/327)
Smoker	24.6% (119/494)	26.1% (84/322)
Hypertension	77.1% (384/498)	72.2% (236/327)
Heart disease	43.0% (214/498)	38.5% (126/327)
COPD	18.2% (91/498)	15.0% (49/327)
Emphysema	9.0% (45/498)	8.3% (27/327)
Afib	7.4% (37/498)	5.8% (19/327)
High cholesterol	63.1% (314/498)	58.7% (192/327)
Obesity	14.1% (70/498)	7.0% (23/327)
Diabetes	33.9% (169/498)	26.6% (87/327)
Stroke	28.1% (140/498)	26.9% (67/327)
Carotid disease	48.5% (243/501)	50.2% (164/327)
Snorer	16.0% (80/501)	13.2% (43/327)

Afib = atrial fibrillation; COPD = chronic obstructive pulmonary disease.

Statistical Analysis

The entire cohort of patients was analyzed. Associations between bilateral carotid disease and smoking, hypertension, heart disease, high cholesterol, diabetes, and stroke were evaluated using χ^2 tests for two-by-two tables. The relationship of snoring with carotid disease was examined using a linear logistic regression analysis. The previously mentioned covariates were included in the model. Additional subgroup analysis was performed on those patients identified as snorers without any history of OSA.

RESULTS

Of 501 study patients, the average age was 68.8 ($\pm$ 9.5) years and 78% were male. Demographic data are shown in Table I. A total of 243 patients with carotid disease were identified (Fig. 1). Those who smoked ($P = .019$), had hypertension ($P = .001$), heart disease ($P = .001$), hypercholesterolemia ($P = .001$), stroke ($P = .001$), or diabetes ($P = .001$) all had significantly increased rates of carotid disease based on a χ^2 test of each condition individually.

Among those patients with carotid disease, 21% (n = 51) were found to be snorers. Only 11% (n = 29) of patients were snorers in the non–carotid disease cohort. A logistic regression analysis of snorers alone found that they had a significantly increased odds (2.1) of having carotid disease ($P = .003$) over nonsnorers. To ensure this relationship was not confounded by the six covariates,

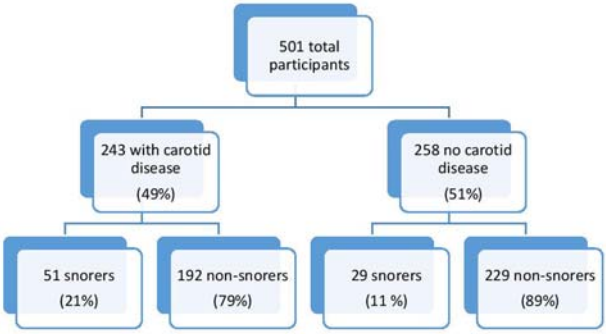

Fig. 1. Breakdown of all participants by snoring status and carotid disease. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

these variables were adjusted for in a multivariate logistic regression which was significant ($P = .0037$, odds ratio [OR]: 1.74) for snorers having carotid disease.

After exclusion of all patients thought to have OSA based on self-reported history of OSA or CPAP use, 327 patients remained (Fig. 2). Among this group, 164 patients had carotid disease. An individual who smoked ($P = .031$), had hypertension ($P = .002$), heart disease ($P = .001$), hypercholesterolemia ($P = .001$), stroke ($P = .001$), or diabetes ($P = .001$) all had significantly increased rates of carotid disease based on a χ^2 test of each condition individually. A total of 17% (n = 28) of patients with carotid disease were primary snorers, whereas only 9% (n = 15) of patients in the non–carotid disease cohort were primary snorers.

Logistic regression analysis of this reduced cohort found snorers to be at significantly higher risk ($P = .038$, OR: 2.03) than nonsnorers of having carotid disease. This significant effect did not hold up when we adjusted the logistic regression model by adding in the six covariates. The OR for snorers having carotid disease was reduced to 1.59, which was not significant ($P = .205$). However, snorers were found to be at significantly increased risk of bilateral carotid disease ($P = .005$, OR: 2.78). This relationship was maintained when we adjusted the logistic regression by adding the covariates into the model ($P = .030$, OR: 2.30).

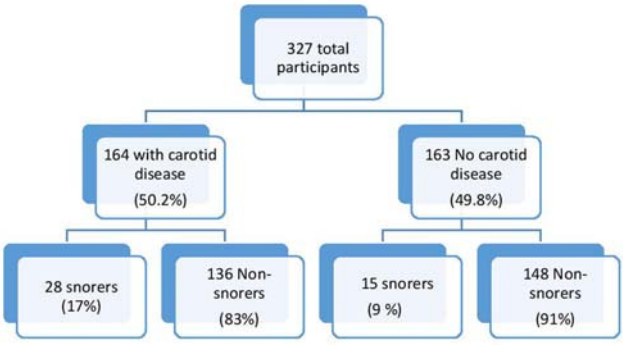

Fig. 2. Breakdown of participants, excluding patients with self-reported sleep apnea. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

DISCUSSION

Recently, there has been increasing interest as to the possible adverse health risks associated with primary snoring and its role in the continuum of sleep-disordered breathing. Although the relationship between OSA and a variety of other medical conditions has been well established,[12] the effect of primary snoring is currently being studied. Because primary snoring has not been recognized as a clinically significant medical condition, insurance companies generally do not pay for procedures or medical devices to treat snoring.

A growing body of evidence suggests that primary snoring is not as harmless as previously thought. The majority of investigations focus on the relationship of snoring to the cardiovascular system. Although the exact mechanism is not fully understood, several theories have been proposed. Evidence from animal models serves as a starting point for a possible pathophysiologic mechanism.[7,13] A proposed mechanism is that snoring causes vibration of the pharyngeal walls and associated structures. The proximity of the carotid bifurcation to the lateral pharyngeal wall is such that it is likely exposed to these vibrations. The vibratory stimuli may cause pathologic changes to the endothelium of proximate vessels, which in turn may lead to an inflammatory cascade ultimately causing intima-media thickness and subsequent atherosclerosis.

A recent study by Lee et al. found that snoring sounds may cause carotid wall thickening, as shown by ultrasound measurement of CCA intima-media thickness.[14] In fact, the specific frequencies of 0 to 20 Hz and 652 to 1,500 Hz correlated most with CCA intima-media thickening, which suggests that the etiology of the thickening is likely more complex and multifactorial. Cicero et al. used the augmentation index and pulse wave velocity, both considered gold-standard measures for vascular aging, to show an association between self-reported snoring, with or without sleep apnea, and arterial stiffness.[15]

The current study may add to the conclusion that snoring, with or without sleep apnea, acts to predispose patients to clinically relevant carotid artery disease. Although previous studies have used a variety of metrics to measure the effect on the vascular system, we aimed to use the gold standard of carotid duplex for diagnosis of carotid artery disease. The underlying mechanisms and physiologic changes in the carotid vasculature have been well established. Given that the decision whether to intervene surgically on a patient is based on carotid duplex results, we felt that evaluating this metric would provide additional clinical significance.

There are some inherent weaknesses in our study. Snoring and sleep apnea are both being captured via patient self-reporting. In large integrated health systems, patients are generally aware if they have been assigned a diagnosis of sleep apnea. Additionally, if a patient is actively using CPAP, then we felt that this is enough evidence that they have sleep apnea, especially given that CPAP can only be obtained by prescription. As such, we felt that the use of a self-reported diagnosis

is indicative of a diagnosis of sleep apnea. Patient self-reported data for snoring have been used in many studies evaluating health outcomes for snoring. Although this has become well accepted in large cohort analyses, it does lack the precision of sleep study recordings. However, because snoring may exhibit nightly variation depending on sleep position, social habits, and sleep stage, the sleep outcomes survey, a validated measure, may be a more accurate representation of snoring status.

Several possibilities exist for additional research in this area. The nature of snoring in patients exhibiting severe carotid occlusive disease should be analyzed. Severity of snoring may be a combination of both duration and volume. Findings in the carotid arteries also raise the possibility of similar findings in the microvasculature of the head and neck. Although endothelial damage due to vibratory effects is a plausible mechanism, the true relationship is likely more complicated. In fact, a study of patients occupationally exposed to chronic vibration showed elevated inflammatory markers (serum intercellular adhesion molecule-1 level) and impaired smooth muscle response in the skin blood vessels at the fingertips.[16]

CONCLUSION

The current study shows that patients with OSA and snoring were more likely to have evidence of carotid artery disease on carotid duplex ultrasonography. Additionally, patients with primary snoring were shown to be more likely to have bilateral carotid artery disease, even when controlling for the known risk factors of smoking, hypertension, heart disease, stroke, diabetes and hypercholesterolemia. These findings add to the growing body of literature showing an association between snoring and OSA and carotid artery disease. Given the high population prevalence of snoring and sleep apnea, we believe this area requires additional study as a risk factor for carotid artery disease.

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