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ORIGINAL RESEARCH

Snoring Sound Characteristics are Associated with Common Carotid Artery Profiles in Patients with Obstructive Sleep Apnea

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Background: Obstructive sleep apnea (OSA) and snoring have been reported to be modifiable risk factors for thick carotid intima-media thickness (CIMT) and carotid atherosclerosis, which are closely linked to cardiovascular disease.

Methods: This cross-sectional study prospectively recruited 70 participants with OSA and without a history of carotid artery disorder, who primarily sought surgical Intervention. OSA and snoring were assessed with the Epworth Sleepiness Scale, Snore Outcomes Survey, polysomnography, and snoring sound recording. The carotid arteries were evaluated with ultrasonography and divided into three types of carotid artery profiles (normal carotid artery, thick CIMT, or significant carotid atherosclerosis). Multivariate linear/logistic/categorical regressions were performed with the forward selection approaches/logistic least absolute shrinkage and selection operator, as appropriate.

Results: Normalized snoring sound energy (301–850 Hz) was independently associated with the carotid intima-media thickness (regression coefficient [β] = 0.01, standard error [SE] = 0.004, $P = 0.03$; $R^2 = 0.067$) and type of carotid profile (β = 0.40, SE = 0.09, $P < 0.001$; $R^2 = 0.156$). Normalized snoring sound energy (4–300 Hz) (β = −0.10, SE = 0.04, $P = 0.01$) and female sex (β = 1.90, SE = 0.94, $P = 0.04$) were independently related to the presence of carotid stenosis ($R^2 = 0.159$). The optimal regression model of the type of carotid artery profile included normalized snoring sound energy (301–850 Hz) (β = 0.33, SE = 0.14, $P = 0.03$), snoring time (β = 0.26, SE = 0.13, $P = 0.047$), female sex (β = 0.26, SE = 0.13, $P = 0.047$), and increased age (β = 0.20, SE = 0.10, $P = 0.04$) under the control of the Snore Outcomes Survey score, 3% oxygen desaturation index, snoring sound energy (4–1500 Hz), normalized snoring sound energy (851–1500 Hz), cigarette smoking, and hyperlipidemia ($R^2 = 0.427$).

Conclusion: Our findings suggested that snoring sound characteristics are associated with carotid artery profiles among early OSA patients who cannot be noticed by ultrasound because organic changes of the carotid artery have not yet started. Future studies are warranted to verify the clinical significance of the results.

Keywords: atherosclerosis, common carotid artery, categorical regression, obstructive sleep apnea, snoring, ultrasound

Introduction

Atherosclerotic cardiovascular disease (CVD), mainly comprising coronary heart disease and cerebrovascular disease, is one of the most important causes of morbidity and premature death worldwide.[1–3] Thick carotid intima-media thickness (CIMT) and carotid atherosclerosis are well-documented risk factors for CVD,

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along with hypertension, diabetes mellitus (DM), cigarette smoking, and hyperlipidemia.[4]

Epidemiological studies indicate that patients with obstructive sleep apnea (OSA) have increased CIMT and subclinical atherosclerosis.[5–8] OSA is associated with an increased incidence and progression of CVD.[9,10] From a meta-analysis, long-term continuous positive airway pressure (CPAP) therapy significantly reduced CIMT in patients with severe OSA.[11] However, an investigation by McEvoy et al did not support that CPAP prevented cardiovascular events in patients with moderate-to-severe OSA and established CVD.[12] Identification and early intervention for OSA patients who are at-risk of future atherosclerotic CVD remain an important yet challenging clinical issue.

Snoring is a cardinal and probably also the most notable symptom of OSA. It negatively affects the quality of life of the patients. Previous studies suggest that snoring sound energy (SSE) is associated with structural pathogenic factors, disease severity, and treatment response.[13–15] Snoring-associated vibration energy can be transmitted from the upper airway lumen to the peri-pharyngeal tissues and then across the carotid artery wall to the lumen.[16,17] In animal models, snoring vibration of the peri-carotid tissue induced endothelial dysfunction[18] and resulted in a depression of baroreflex sensitivity.[19] Both endothelial and autonomic dysfunctions promote carotid atherosclerosis in humans.[20,21]

Kim et al reported an independent association between snoring and increased CIMT.[15] Lee et al further demonstrated that CIMT was correlated with SSE at some specific frequencies.[22] Notably, features of snoring sounds differ largely within individuals. Therefore, normalization of SSEs is essential to ensure comparability between different subjects regardless of pre-existing heterogeneity. SSE-based technology may be beneficial to risk stratification for carotid artery disorders among patients with OSA. However, investigations on the field are rare, evidence scarce, and conclusions unclear.

We hypothesized that OSA severity and SSE were associated with an abnormal carotid artery profile. In this study, the first aim was to investigate differences in polysomnographic parameters and frequency-specific SSE between patients with normal carotid arteries, thick CIMT, or carotid atherosclerosis. The second aim was to identify independent factors predicting the carotid artery profile among patients with OSA.

Materials and Methods

Data Availability Statements

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data can be shared at reasonable request to the corresponding author.

Study Design and Subjects

This prospective cross-sectional study was approved by the Institutional Review Board at the Chang Gung Medical Foundation (No. 201700902A3; date of approval: 26 July 2017), and all procedures were conducted in compliance with the Declaration of Helsinki 1975. Written informed consent was obtained from all participants. Consecutive patients who sought surgical intervention at the clinics of Department of Otorhinolaryngology, Head and Neck Surgery, Chang Gung Memorial Hospital, Taoyuan, Taiwan because of typical OSA symptoms (habitual snoring, witnessed sleep apnea, or excessive daytime sleepiness) were recruited between May 2018 and October 2020. The inclusion criteria were: (1) age between 20 and 59 years; (2) body mass index (BMI) between 18 and 35 kg/m^2; and (3) willingness to participate in this study after it had been explained in detail. The exclusion criteria were (1) history of upper airway surgery such as uvulopalatopharyngoplasty; (2) contraindications for OSA surgery, such as established CVD with or without medication and psychiatric disorders; and (3) history of abnormal carotid artery profile such as thick IMT, carotid plaque, or carotid atherosclerosis. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed.[23]

Clinical Variables and Traditional Atherosclerotic CVD Risk Factors

Sex, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and the duration of OSA were recorded. The Epworth Sleepiness Scale (ESS) questionnaire was used to assess daytime sleepiness,[24] and the Snore Outcomes Survey (SOS) questionnaire was used to assess snoring-related health status.[25] Furthermore, traditional atherosclerotic CVD risk factors, including increased age (men, ≥45 years; women, ≥55 years), overweight or obesity (BMI ≥24 kg/m^2), cigarette smoking (previous or current), hypertension, diabetes mellitus (DM), and hyperlipidemia, were also collected.[26–28]

OSA Severity Parameters from Polysomnography

All patients underwent in-laboratory polysomnography (Alice 5, Philips Respironics, MA, USA) in a silent environment.[29] An apnea event was defined as a drop in the peak thermal sensor excursion by ≥90% of the baseline for at least 10 s. Hypopnea was defined as a decrease in the nasal pressure signal excursion by ≥30% for at least 10 s, accompanied by desaturation of 4% or more from the pre-event baseline or an arousal from sleep.[30] Apnea–hypopnea index (AHI), 3% oxygen desaturation index (ODI3), mean pulse oxygen saturation (SpO_2), and minimal SpO_2 were recorded. OSA was defined as obstructive AHI ≥5 events/h.

Snoring Sound Detection and Analysis

In this study, snoring sound detection and polysomnography were performed simultaneously in a well-controlled sleep laboratory setting to ensure a high quality of the data. A portable digital sound recorder with linear pulse-code modulation (PCM-D50, Sony Electronics Inc., Tokyo, Japan) was positioned 100 cm above the participant's head to record snoring sounds. The methodologies of snoring sound detection and analysis have been described in detail in previous studies.[22,29] At least 4 h of snoring sounds were recorded at a sampling rate of 44,100 Hz with a 16-bit analog-to-digital converter for each participant.[14] The frequency power spectrum was created by fast Fourier transformation (range, 4–1500 Hz) with a frequency resolution of 4 Hz. We further analyzed snoring sounds throughout each recording using a 0.25-s time window with no overlapping data. Net snore power was obtained by subtracting the long-term spectrum average of noise from that of each snoring frequency. The snoring index (SI) and snore time ratio (ratio of total snoring time to total sleep time) were analyzed. SSE levels (J/m^3) of various frequency domains were acquired using a specially developed software program (Figure 1A). There were four frequency bands (total, 4–1500 Hz; B1, 4–300 Hz; B2, 301–850 Hz; and B3, 851–1500 Hz).[13,29,31–33] Notably, differences in the total SSE and specific frequency-domain SSEs of between individuals were very heterogeneous. Although snoring intensity was similar in both sexes and seemed not to be affected by AHI, SI was higher in men and in slow wave sleep in adults.[34] As inter-individual comparisons were potentially affected by lack of SSE normalization, the specific frequency-domain normalized SSE (SSE%) was further quantified as the ratio of the frequency-domain SSE to the sum of all frequency-domain SSEs (Figure 1B).

Carotid Artery Evaluation with Ultrasonography

To minimize observer bias, the investigation team members who performed carotid ultrasonography were blinded to the patients' clinical information. With the patient placed in the supine position, images of bilateral common, internal, and bifurcation sites of the carotid arteries were obtained using a B-mode ultrasound system (Philips HDI 5000 System, ATL-Philips, Bothell, USA) and a 5- to 13-MHz vascular

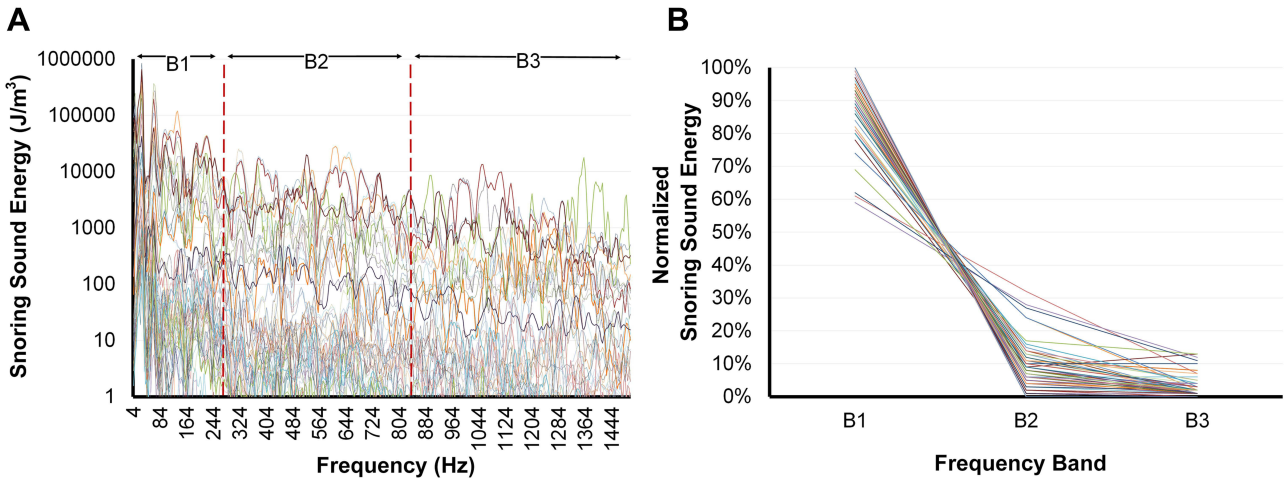

Figure 1 Distribution of long-term energy spectrum of the snoring sounds before and after normalization in 70 adults with obstructive sleep apnea. (**A**), Before normalization, the distributions of all frequency-domains of snoring sound energies were very heterogenous between different subjects. (**B**) After normalization, heterogeneity of all frequency-domains of snoring sound energies had been reduced to evaluate both the amount and characteristics of energy conveyed by snoring. Frequency domain: B1, 4–300 Hz; B2: 301–850 Hz; B3: 851–1500 Hz.

probe. In this study, far-wall CIMT in the distal portion of each common carotid artery (CCA) was measured in the proximal 1 to 2 cm of the carotid bulb in plaque-free areas.[35] The CIMT of the right and left CCAs were measured six times, and all results were averaged for statistical analysis. The American Society of Echography task force recommends that CIMT ≥75th percentile (according to sex and age subgroups for right and left CCAs) was considered "thick CIMT" because of an increased CVD risk.[26,36] The presence of plaque was defined by focal structures infringing into the arterial lumen by at least 1.5 mm or focal narrowing of the vessel wall of >50% relative to adjacent segments.[26,37,38] The degree of carotid stenosis (normal: 0% stenosis of the CCA luminal diameter; mild: <50% stenosis; moderate: 50–69% stenosis; severe: 70–99% stenosis) were measured.[37,38] Herein, thick CIMT indicated subclinical carotid atherosclerosis while significant carotid atherosclerosis was defined if there was the presence of plaque or carotid stenosis, which could be a potential source of embolic strokes. Therefore, participants were further categorized into three carotid artery profiles: 'normal carotid arteries (ie, none of thick CIMT or carotid plaque), "thick CIMT" (ie, solitary thick CIMT without carotid plaque or stenosis), or 'significant carotid atherosclerosis' (ie, having carotid plaque or stenosis).

Statistical Analysis

The main outcome measure was the type of the carotid artery profile. Using the D'Agostino and Pearson normality test, most of the variables were not normally distributed. Therefore, those non-normally distributed continuous variables were transformed to normal using a two-step approach: the fractional rank and inverse-normal transformation.[39] Thereafter, continuous data are presented as means and standard deviations for normally distributed variables or medians and interquartile ranges (IQR) for skewed variables and were compared using the oneway analysis of variance test followed by Tukey post hoc test for independent samples, as appropriate. Categorical data are presented as numbers and percentages and were compared using X^2 test. The associations between continuous and continuous variables or between continuous and binary variables were investigated using the Pearson correlation test or Point-Biserial correlation test, as appropriate. Spearman correlation test was performed to examine the associations between multi-categorical variables and continuous/binary variables.

The associations between the CIMT/presence of carotid stenosis were further investigated using multivariate linear/logistic regression models. Besides, the variables associated with the type of the carotid artery profile were analyzed using multivariate categorical regression models. Incorporation of external information and the sign of regression coefficients with full models, including important variables with significance levels of 0.50 in univariate analyses, were further assessed using multivariate linear/logistic/categorical regression models.[40] Regression coefficients were optimally reduced with the forward selection approaches for the multivariate linear/logistic regression models or the logistic least absolute shrinkage and selection operator (LASSO) for multivariate categorical regression models.[41] The standard errors (SE) of the regression coefficients (β) were obtained using the bootstrap resampling (*n* of samples = 50; 1000 runs). Two-tailed *P*-values <0.05 were considered to be statistically significant. All statistical analyses were performed using SPSS software (version 25.0; International Business Machines Corp., Armonk, NY, USA) and Graph Pad Prism 9.0 for Windows (Graph Pad Software Inc., San Diego, CA, USA).

Results

Clinical Characteristics of Patients with OSA

There were 167 consecutive adults who primarily sought surgical intervention due to habitual snoring, witnessed sleep apnea, or excessive daytime sleepiness during the study period (Figure 2). Fifty-three patients did not meet the inclusion criteria. Furthermore, 17 patients were excluded due to a history of upper airway surgery (*n* = 6), contraindications for OSA surgery (*n* = 7), or a history of abnormal carotid artery profile (*n* = 4). Moreover, two patients with simple snoring (obstructive AHI <5 events/h), 20 patients with inadequate quality of snoring sound data, and five patients with lack of ultrasonography were not included for further statistical analysis.

Therefore, a total of 62 (89%) men and eight (11%) women with a median age of 39 (IQR, 33–48) years and a median BMI of 27.3 (IQR, 25.6–29.8) kg/m^2 were recruited (Table 1). The median SBP was 124 (IQR, 116–134) mmHg and mean DBP was 75.0 ± 11 mmHg. The median ESS scale was 13 (IQR, 10–18), and the mean SOS score was 36.9 ± 10.0.

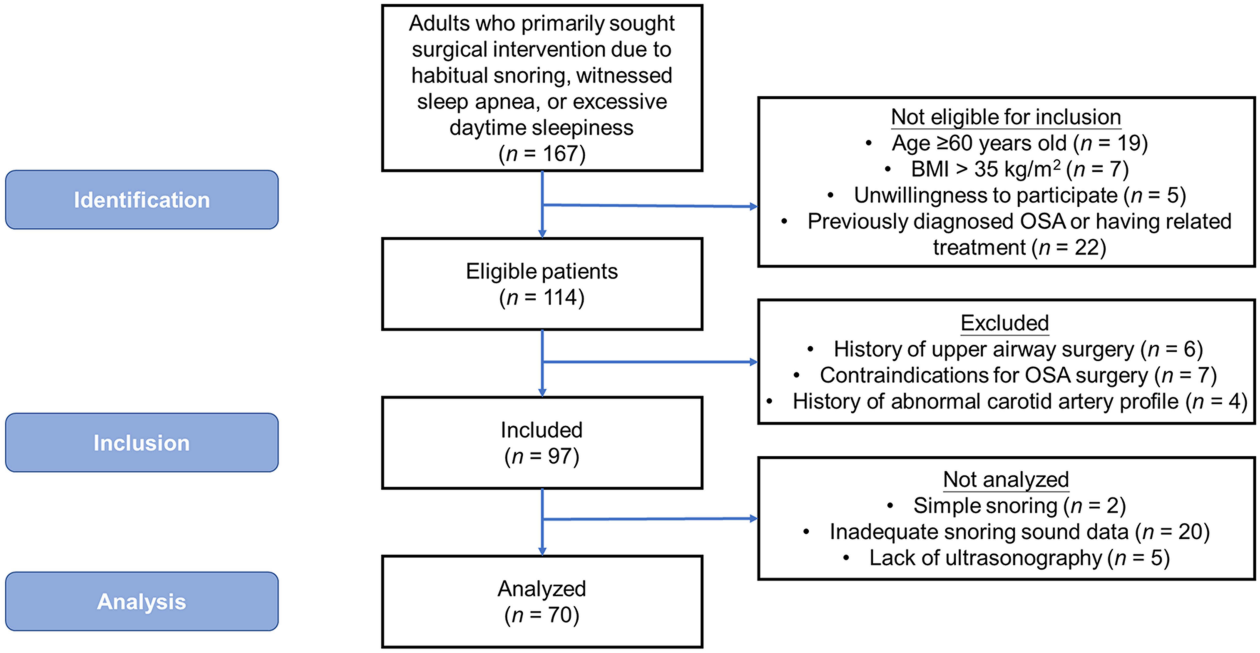

Figure 2 Flow diagram of study participants.
Abbreviations: BMI, body mass index; OSA, obstructive sleep apnea.

Twenty (29%) patients had an increased age; 61 (87%) had overweight or obesity; 23 (33%) were previous or current smokers; 12 (17%) had hypertension; 16 (23%) had hyperlipidemia. None had a known diagnosis of DM.

The average AHI, ODI, mean SpO_2, and minimal SpO_2 were 62.5 (IQR, 26.0–79.7) events/h, 49.6 (IQR, 17.0–68.8) events/h, 95% (IQR, 93–95%), and 84% (IQR, 77–88%), respectively.

The median SI, snoring time ratio, SSE-total, SSE-B1, SSE-B2, SSE-B3, SSE%-B1, SSE%-B2, and SSE%-B3 were 49.7 (IQR, 21.7–197.2) events/h, 2.7% (IQR, 1.3–8.1%), 255.7 (IQR, 56.1–6795.2) J/m^3, 237.8 (IQR, 48.4–6384.0) J/m^3, 8.6 (IQR, 2.8–302.1) J/m^3, 3.6 (IQR, 0.5–136.7) J/m^3, 91.9% (IQR, 85.7–97.0%), 6.4% (IQR, 2.4–10.6%), and 1.4% (IQR, 0.6–3.7%), respectively.

The median CIMT of the overall cohort was 0.60 (IQR, 0.51–0.77) mm. Twenty-two (31%) participants had normal carotid artery, 22 (31%) patients had solitary thick CIMT (ie, subclinical carotid atherosclerosis), and 26 (37%) patients had significant carotid atherosclerosis (solitary carotid plaque [$n = 2$], thick CIMT with carotid plaque [$n = 3$], and solitary carotid stenosis [$n = 21$]). The median CIMTs of these three subgroups were 0.50 (IQR, 0.43–0.53) mm, 0.61 (IQR, 0.55–0.75) mm, and 0.78 (IQR, 0.71–0.91 mm), respectively. Among the patients with significant carotid atherosclerosis, eleven (42%) had mild carotid stenosis, 14 (54%) had moderate stenosis, and one (4%) had severe carotid stenosis.

The mean duration of OSA was 2.02 ± 0.96 years. The mean time interval between carotid ultrasound and polysomnography was 22.3 ± 14.6 days.

Differences in Clinical Characteristics Across Three Subgroups

Differences in SBP, DBP, snoring time ratio, SSE%-B1, and SSE%-B2 were significant across three subgroups (Table 1). Notably, the thick CIMT subgroup had significantly higher SBP, DBP, and snoring time ratio than the normal carotid artery subgroup. Furthermore, the significant carotid atherosclerosis subgroup had a significantly lower SSE%-B1 and a significantly higher SSE%-B2 than the normal carotid artery subgroup. Differences in sex, age, BMI, cigarette smoking, hypertension, hyperlipidemia, DM, ESS, SOS, AHI, ODI3, mean SpO_2, minimal SpO_2, and other six snoring sound analysis parameters across the three subgroups were not statistically significant.

Table 1 Characteristics of the Study Population and Comparisons Among Participants with Different Carotid Artery Profile

Characteristics	All Participants (n = 70)	Normal Carotid Arteries (n = 22)	With Thick CIMT (n = 22)	With Carotid Atherosclerosis (n = 26)	*P*-value[a]
Clinical parameters					
Male, n (%)	62 (89)	21 (96)	20 (91)	21 (81)	0.28
Age, y	39 (33–48)	37 (32–43)	41 (33–45)	43 (32–50)	0.29
BMI, kg/m^2	27.3 (25.6–29.8)	26.0 (24.2–28.6)	27.8 (26.3–31.3)	28.7 (26.7–29.5)	0.21
SBP, mmHg	124 (116–134)	122 (115–126)[b]	132 (123–150)[b]	124 (113–137)	0.01
DBP, mmHg	75.0 ± 11.3	71.7 ± 8.9[b]	80.3 ± 10.5[b]	73.2 ± 12.6	0.02
ESS, scale	13 (10–18)	14 (10–17)	13 (9–19)	13 (10–18)	0.86
SOS, score	36.9 ± 10.0	39.6 ± 9.9	35.3 ± 9.3	35.7 ± 9.2	0.25
Duration of OSA, y	2.02 ± 0.96	2.13 ± 1.09	2.02 ± 0.93	1.9 ± 0.88	0.78
Traditional atherosclerotic cardiovascular disease risk factors					
Increased age, n (%)	20 (29)	4 (18)	7 (35)	9 (35)	0.42
Overweight or obesity, n (%)	61 (87)	18 (82)	19 (86)	24 (92)	0.55
Cigarette smoking, n (%)	23 (33)	10 (46)	6 (26)	7 (27)	0.32
Hypertension, n (%)	12 (17)	2 (9)	6 (27)	4 (15)	0.27
DM, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	–
Hyperlipidemia, n (%)	16 (23)	2 (9)	6 (27)	8 (31)	0.17
Polysomnographic parameters					
AHI, events/h	62.5 (26.0–79.7)	52.7 (18.2–74.9)	69.3 (37.3–82.9)	48.9 (19.3–83.9)	0.24
ODI3, events/h	49.6 (17.0–68.8)	44.9 (11.0–68.9)	61.0 (26.2–72.7)	33.2 (11.8–68.0)	0.09
Mean SpO_2, %	95 (93–95)	95 (93–95)	95 (93–95)	95 (94–95)	0.74
Minimal SpO_2, %	84 (77–88)	84 (78–88)	79 (74–87)	84 (79–89)	0.19
Snoring sound analysis					
Snoring index, events/h	49.7 (21.7–197.2)	82.0 (32.2–256.3)	49.0 (15.7–115.2)	39.7 (21.3–187.5)	0.49
Snoring time ratio, %	2.7 (1.3–8.1)	2.3 (1.0–18.2)[b]	3.2 (1.8–6.5)[b]	2.7 (1.1–7.5)	0.02
SSE-total, J/m^3	255.7 (56.1–6795.2)	199.5 (49.6–5704.4)	841.0 (43.2–11,617.5)	70.1 (53.5–5160.2)	0.23
SSE-B1, J/m^3	237.8 (48.4–6384.0)	176.7 (45.7–5437.5)	834.0 (94.0–10,499.4)	65.4 (42.8–4694.5)	0.19
SSE-B2, J/m^3	8.6 (2.8–302.1)	5.8 (1.4–244.1)	43.3 (2.7–658.3)	8.6 (3.1–328.3)	0.31
SSE-B3, J/m^3	3.6 (0.5–136.7)	2.8 (0.3–41.5)	12.9 (0.6–215.3)	2.2 (0.5–40.1)	0.27
SSE%-B1, %	91.9 (85.7–97.0)	93.5 (89.7–99.5)[b]	91.1 (82.0–95.4)	90.7 (82.7–93.5)[b]	0.04
SSE%-B2, %	6.4 (2.4–10.6)	4.7 (0.4–8.5)[b]	6.6 (3.2–12.4)[b]	7.3 (4.3–11.3)[b]	0.01
SSE%-B3, %	1.4 (0.6–3.7)	0.7 (0.2–2.4)	1.9 (0.6–5.5)	1.4 (0.7–3.1)	0.08

Notes: Continuous data are displayed as means ± standard deviations or medians (interquartile ranges), as appropriate; categorical data are expressed as numbers (percent). [a]Differences between groups were compared using the oneway analysis of variance (for mean or normalized mean), and X^2 test (for percentage). [b]The Fisher's least significance test was performed between normal carotid artery and thick CIMT subgroups or normal carotid artery and carotid atherosclerosis subgroups or thick CIMT and carotid atherosclerosis subgroups.

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; ESS, Epworth Sleepiness Scale; ODI3, 3% oxygen desaturation index; SBP, systolic blood pressure; SOS, Snore Outcomes Survey; SpO_2, pulse oxygen saturation; SSE%, normalized snoring sound energy.

Associations Between CIMT and Variables of Interest

The CIMT was significantly and weakly associated with the SSE%-B2 (r = 0.26, P = 0.03) using the Pearson correlation test. For reducing the likelihood of overfitting, the variables with P <0.50 such as age (r = 0.15, P = 0.23), BMI (r = 0.18, P = 0.15), SBP (r = 0.12, P = 0.34), DBP (r = 0.11, P = 0.38), SOS score (r = −0.19, P = 0.12), the duration of OSA (r = 0.10, P = 0.42), AHI (r = 0.11, P = 0.36), SI (r = −0.11, P = 0.38), snoring time ratio (r = 0.18, P = 0.24), SSE-total (r = −0.13, P = 0.28), SSE-B1 (r = −0.13, P = 0.30), SSE%-B1 (r = −0.20, P = 0.10), and SSE%-B3 (r = 0.19, P = 0.12), using the Pearson correlation test, and female sex (r = 0.18, P = 0.13), using the Point-Biserial correlation test, were included for multivariate linear analysis.[41] Using the forward selection methods, the SSE%-B2 was the independent variables related to CIMT (β = 0.01, SE = 0.004, P = 0.03) (R^2 = 0.067). The relationship between the SSE%-B2 and CIMT remained to be significant (β = 0.01, SE = 0.004, P = 0.04) after adjustment for increased age (β = 0.09, SE = 0.05, P = 0.07), overweight or obesity (β = 0.04, SE = 0.07, P = 0.60), cigarette smoking (β = −0.01, SE = 0.05, P = 0.78), hypertension (β = 0.04, SE = 0.06, P = 0.53), and hyperlipidemia (β = 0.04, SE = 0.05, P = 0.46) (R^2 = 0.156).

Associations Between the Presence of Carotid Stenosis and Variables of Interest

The presence of carotid stenosis was significantly related to SSE%-B2 (r = 0.26, P = 0.03) using the Point-Biserial correlation test. Herein, female sex (r = 0.20, P = 0.10), age (r = 0.16, P = 0.20), SBP (r = −0.09, P = 0.48), DBP (r = −0.10, P = 0.40), SOS (r = −0.09, P = 0.48), ODI3 (r = −0.17, P = 0.18), minimal SpO_2 (r = 0.10, P = 0.41), the duration of OSA (r = −0.09, P = 0.46), SSE-total (r = −0.16, P = 0.20), SSE-B1 (r = −0.18, P = 0.15), SSE%-B1 (r = −0.23, P = 0.06), and SSE%-B3 (r = 0.18, P = 0.13) were additionally included for multivariate logistic regression analysis. Using the forward selection methods, female sex (β = 1.81, SE = 0.85, P = 0.03) and SSE%-B1 (β = −0.08, SE = 0.03, P = 0.02) were the independent variables related to the presence of carotid stenosis (R^2 = 0.159). The significant relationships of the presence of carotid stenosis with female sex (β = 1.90, SE = 0.94, P = 0.044) and SSE%-B2 (β = −0.10, SE = 0.04, P = 0.01) persisted after adjustment for increased age (β = 0.85, SE = 0.66, P = 0.20), overweight or obesity (β = 1.40, SE = 1.04, P = 0.18), cigarette smoking (β = 0.01, SE = 0.63, P = 0.99), hypertension (β = −0.60, SE = 0.83, P = 0.47), and hyperlipidemia (β = 0.68, SE = 0.66, P = 0.30) (R^2 = 0.234).

Associations of the Type of the Carotid Artery Profile with Variables of Interest

The carotid artery profiles were further quantified as type 1 (normal carotid artery), type 2 (thick CIMT), and type 3 (significant carotid atherosclerosis) according to the potential of future CVD.[4] The type of the carotid artery profile was significantly and weakly associated with the SSE%-B1 (r = −0.28, P = 0.02), SSE%-B2 (r = 0.34, P = 0.004), and SSE%-B3 (r = 0.25, P = 0.04) using the Spearman correlation test. For avoiding overfitting, the variables with P <0.50 and traditional atherosclerotic CVD risk factors were additionally included for multivariate categorical analysis. Therefore, female sex (r = 0.19, P = 0.11), age (r = 0.19, P = 0.12), BMI (r = 0.11, P = 0.37), SOS score (r = −0.21, P = 0.09), ODI3 (r = −0.09, P = 0.47), SI (r = −0.12, P = 0.34), snoring time ratio (r = 0.17, P = 0.25), SSE-total (r = −0.12, P = 0.33), and SSE-B1 (r = −0.13, P = 0.28), increased age (r = 0.15, P = 0.22), overweight or obesity (r = 0.13, P = 0.28), cigarette smoking (r = −0.16, P = 0.19), hypertension (r = 0.06, P = 0.62), and hyperlipidemia (r = 0.21, P = 0.08) were further selected for regression models. Moreover, overlapping information (age, BMI) was removed from regression analysis.[40]

Table 2 shows data adjusted for all the selected variables including specific variables and traditional atherosclerotic CVD risk factors. Using the LASSO methods for actively selecting from a potentially multicollinear set of variables in the regression,[41] the optimal categorical regression model of the type of the carotid artery profile included female sex, SOS score, ODI3, snoring time ratio, SSE-total, SSE%-B2, SSE%-B3, increased age, cigarette smoking, and hyperlipidemia (R^2 = 0.427) (Figure 3). Among them, the female sex (β = 0.26, SE = 0.13, P = 0.047), increased age (β = 0.20, SE = 0.10, P = 0.04), snoring time ratio (β = 0.26, SE = 0.13, P = 0.047), and SSE%-B2 (β = 0.33, SE = 0.14, P = 0.03) were significantly and independently related to the type of the carotid artery profile. The most parsimonious model within one standardized error included only the SSE%-B2 (β = 0.40, SE = 0.09, P < 0.001; R^2 = 0.156).

Table 2 The Estimated Coefficients for Logistic Least Absolute Shrinkage and Selection Operator (LASSO) Regression Between Studied Variables and Traditional Atherosclerotic Cardiovascular Disease Risk Factors with the Type of the Carotid Artery Profile

Variables	LASSO Coefficient	Regression Coefficient	Bootstrap (1000 Runs) Estimate of Standard Error	*P*-value
Female sex	0.15	0.26	0.13	0.047
SOS score	−0.08	−0.14	0.16	0.37
ODI3	−0.01	0.08	0.16	0.61
Increased age	0.08	0.20	0.10	0.04
BMI ≥24 kg/m^2	0	–	–	–
No cigarette smoking	0.02	0.12	0.10	0.21
Hypertension	0	–	–	–
Hyperlipidemia	0.09	0.12	0.10	0.21
Snoring time ratio	0.08	0.26	0.13	0.047
SSE-total	−0.12	−0.27	0.15	0.08
SSE-B1	0	–	–	–
SSE%-B1	0	–	–	–
SSE%-B2	0.28	0.33	0.14	0.026
SSE%-B3	0.07	0.17	0.20	0.40

Abbreviations: BMI, body mass index; ODI3, 3% oxygen desaturation index; SOS, Snore Outcomes Survey; SSE, snoring sound energy; SSE%, normalized snoring sound energy.

Discussion

The present study conducted a detailed investigation on the relationships between OSA severity, snoring sound characteristic, and carotid artery profile based on a hospital-based sample. We discovered that the SSE%-B2 was associated with CIMT, independently of traditional atherosclerotic CVD risk factors (Figure 4). In contrast, SSE%-B1 and female sex were related to the presence of carotid stenosis with or without adjustment for traditional atherosclerotic CVD risk factors. Furthermore, the increased SSE%-B2, snoring time ratio, female sex, and increased age were independent risk factors for the abnormal carotid artery profile after adjustment for the other six covariances with the optimal performance. Interestingly, polysomnographic parameters, including AHI, mean SpO_2, and minimal SpO_2, were not related to carotid sonographic parameters in patients with OSA. In most clinical settings, carotid sonography is not a routine exam for patients with early OSA with subclinical carotid artery disease. Our findings suggest that this non-invasive snoring sound analysis has the potential to help the risk stratification of carotid artery disease for this population.

An increasing number of studies have investigated the relationships between OSA and carotid arteries because of their clinical importance and shared risk factors. Previous studies reported that traditional CVD risk factors seemed less accurate in estimating atherosclerosis for patients with OSA.[42,43] The current study had a few strengths, which enabled us to provide several novel and unique perspectives to the topic and overcame some limitations of the previous works.[15,44,45]

First, the profile of carotid arteries was carefully evaluated and defined. Increased CIMT and carotid atherosclerosis are both well-known risk factors for ischemic stroke.[4,46] Besides, CIMT nonlinearly predicts the risk of CVD events.[47] However, both CIMT and atherosclerosis progress with age, and age-related CIMT growth is not necessarily connected with atherosclerosis.[46,48,49] In this study, we defined "thick CIMT" according to the American Society of Echography Task Force recommendations, which is considered to perform better in predicting cardiovascular events.[26,36] We found that both female sex and increased age were independently related to the high type of the carotid artery profile in patients with OSA.

Second, the effect of snoring was investigated with an intricate and in-depth method. Snoring is an easily recognizable symptom but not easily described and quantified as a parameter. It is usually screened with self-reported questionnaires such as Berlin Questionnaire, STOP-Bang questionnaire, and SOS questionnaire. These tools are convenient and highly accessible, but the data collected are mostly subjective and not ideal for an objective and quantitative evaluation. Previous investigations on the associations between snoring and carotid artery disorder had inconsistent conclusions. Self-reported snoring was demonstrated to be related to subclinical atherosclerosis,[7] high-risk carotid plaque features,[50] or bilateral carotid artery stenosis.[51] However, some research

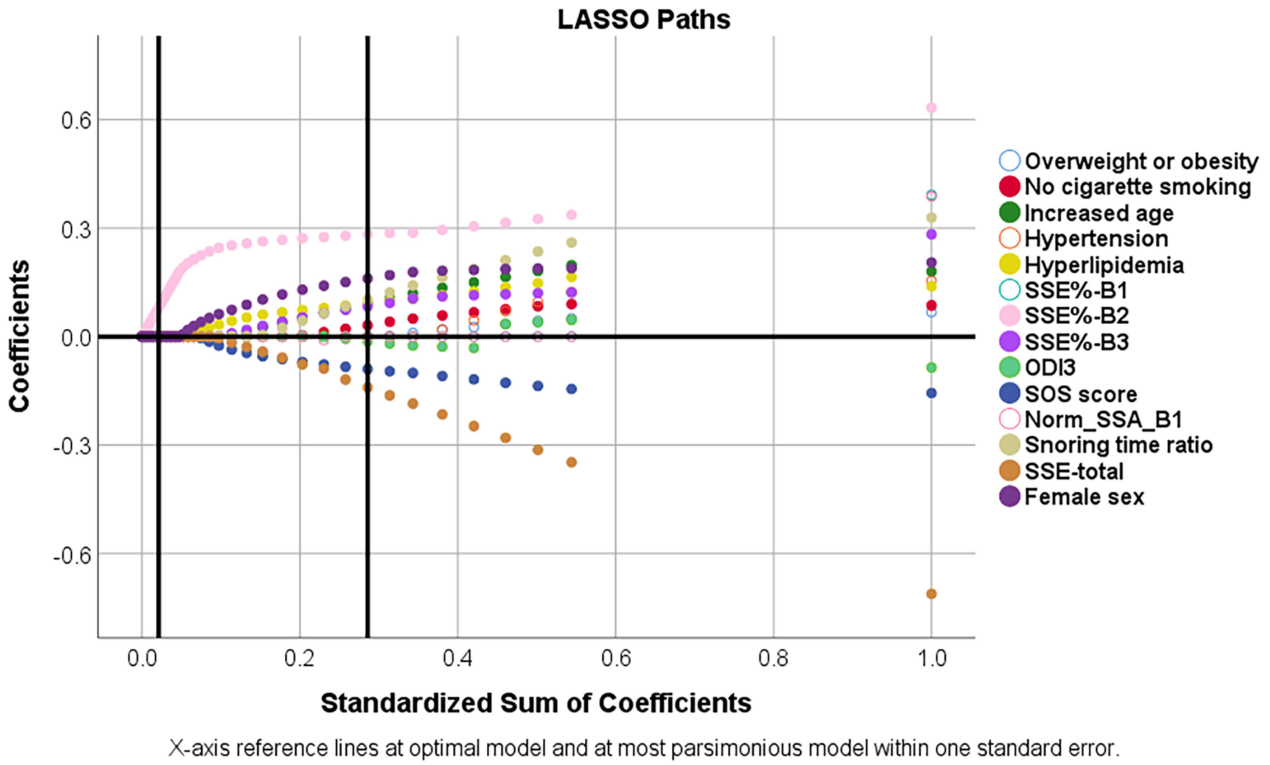

Figure 3 Logistic least absolute shrinkage and selection operator (LASSO) paths for the type of the carotid artery profiles. Fifteen variables, including studied variables and traditional atherosclerotic cardiovascular disease risk factors, were analyzed using the multivariate categorical regression models. X-axis reference lines indicate the optimal model (ten variables) and the most parsimonious model (one variable) within one standard error.

Abbreviations: ODI3, 3% oxygen desaturation index; SOS, Snore Outcomes Survey; SSE, snoring sound energy; SSE%, normalized snoring sound energy.

suggested differently. In a larger cohort study, habitual snoring (≥3 nights/week) was not a risk factor of carotid atherosclerosis.[8] From our results, no significant correlation was found on carotid artery status with SOS, SI, or the duration of OSA.

Based on the hypothesis that the long-term acoustic or vibratory energy of snoring is a possible driving force of endothelial damage of adjacent vessels, a spectrum that demonstrates the energy of snoring sound (either in SSE or SSE%) and snoring time ratio can serve as better parameters for assessing the dose–response effect of snoring on CIMT and carotid atherosclerosis compared to all the other currently used approaches. This has formed the rationale for a series of previous studies.[13–15] In an earlier investigation, we found that full-night SSE-0–20 Hz and SSE-652–1500 Hz, as their snoring sounds recorded in the home environment, were positively associated with CIMT in 15 patients with OSA.[22] In this study, the SSE%-B2 was positively associated with CIMT, the SSE %-B1 was inversely related to the presence of carotid stenosis under the control of the other two covariances, and the SSE%-B2 and snoring time ratio were positively correlated with the type of the carotid artery profile under the control of the other eight covariances. These findings suggested that the SSE might play a less important role than the SSE% and snoring time ratio in a specific population. Noteworthy, the snoring time ratio and type of carotid artery profile were inverted U-shape relationship and SEE%-B1 and SEE%-B2 were a reciprocal relationship (Figure 4). Apparently, these indexes might account for some unexplained causes of the traditional atherosclerotic model. Our results suggested that snoring plays an important role in the thickening wall of the carotid artery, and traditional atherosclerotic risk factors continuously contributed to the formation of atheroma and plaque of the carotid artery in patients with OSA.

Notably, the SSE%-B2 seems to be a novel independent marker for CIMT and type of carotid artery profile. More studies are warranted to prove its effects on the carotid artery wall. The snoring sounds with a peak frequency between 301 Hz and 850 Hz (B2) were linked to epiglottic snores (peak frequency, 490 Hz).[52] Because the epiglottis is anatomically located nearby the CCA, our finding suggested that epiglottic snores might transmit to the CCA and then involve in the

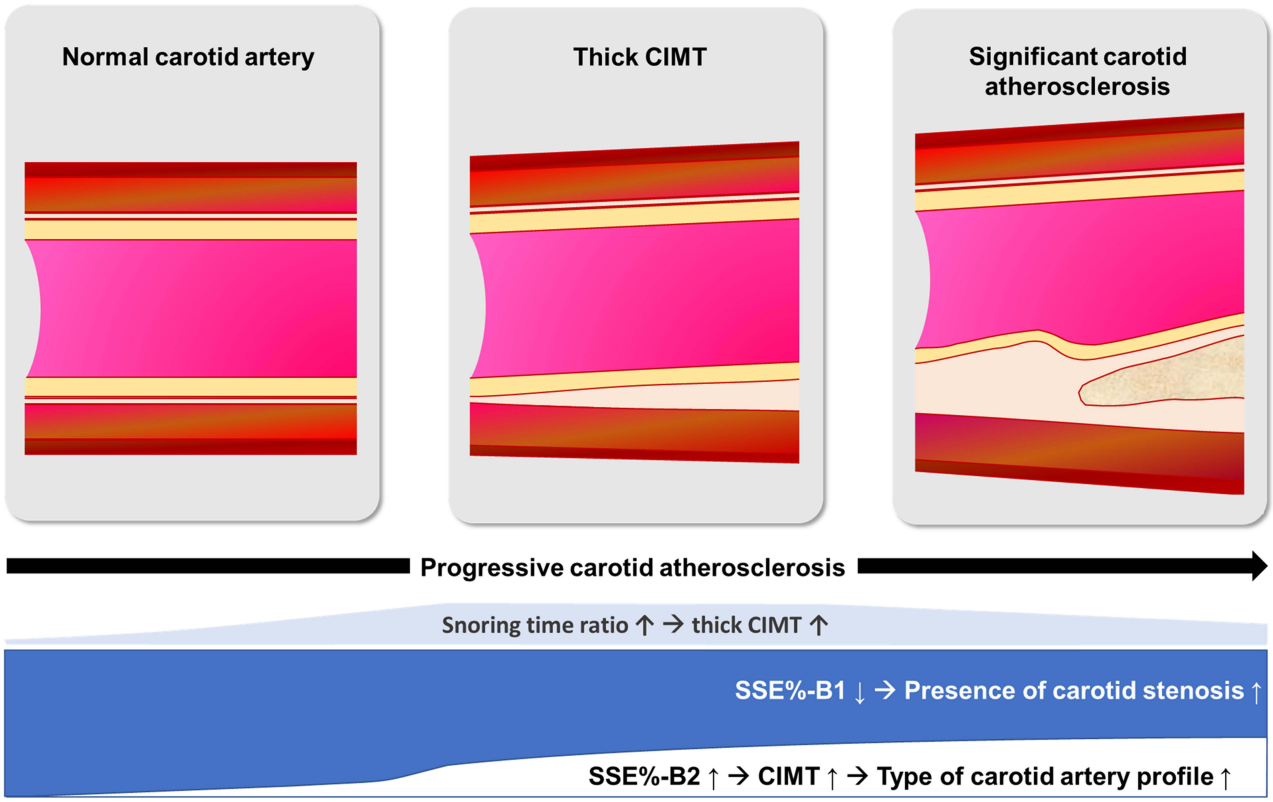

Figure 4 Snoring sound characteristics and carotid atherosclerosis in patients with obstructive sleep apnea.
Abbreviations: B1, 4–300 Hz; B2, 301–850 Hz; CIMT, carotid intima-media thickness; SSE%, normalized snoring sound energy.

development of thick CIMT and carotid atherosclerosis. Furthermore, SSE-B2 has been correlated with oropharyngeal lateral wall collapse, epiglottis obstruction,[29] or tonsil/tongue base obstruction.[53,54] Notably, a high SSE%-B2 does not necessarily mean a high SSE-B2, especially when the SSE-total is small. Therefore, future studies are warranted to investigate whether SSE%-B2 is a possible pathogenic or exacerbating factor effected on the damage of carotid arteries through the lateral wall of the pharynx, either by structural compression, which could disturb blood flow, or repetitive vibrating motions, which could lead to microdamage to the endothelium of the vessels, or both.

The literature has had inconsistent conclusions on whether the clinical presentation or disease severity of OSA is associated with CIMT.[45,55,56] Ghofraniha et al reported a correlation between ESS and CIMT.[57] Zhou et al elucidated that OSA was an independent risk factor for CIMT after adjusting for confounders.[58] However, some other studies found no evidence to support AHI as an independent predictor of CIMT.[59,60] From our data, the ODI3 was partially associated with the type of carotid artery profile, but there were no associations of the carotid artery profile with ESS, AHI, mean SpO_2, or minimal SpO_2.

There were some limitations to this study. First, it was cross-sectional and unable to confirm causal relationships. Longitudinal studies are warranted to examine the long-term effects of OSA severity and snoring on carotid atherosclerosis and CVD events. Second, the subjects of this study were patients in need of surgical treatment for OSA, and this might limit the generalizability of our findings. Although this study was a biased sample towards males, younger age, more severe OSA, and absence of morbid obesity, diabetes, and clinical carotid atherosclerosis because we used convenience sampling, it reflected the truth of an academic otolaryngology center in Taiwan. Noteworthily, CPAP is the first-line treatment for moderate-to-severe OSA;[61] surgical intervention is an alternative treatment for patients who are incompliant or unwilling to CPAP therapy.[62] Third, the sample size was relatively small for multivariate regression models with a lot of variables. In this study, qualitative external information for selection and estimation was used to reduce overfit models in small data sets.[40] Furthermore, the forward

selection approach and LASSO regression analysis was performed to select optimal variables, reduce the variability in the estimates of regression coefficient, improve the prediction error of the model, and increase interpretability.[41] However, further studies with a larger sample size are warranted to thoroughly investigate the role of snoring in the pathogenesis of carotid atherosclerosis among OSA patients at different disease stages and with various treatment plans.

Conclusion

In summary, approximately two-third of early OSA patients had abnormal carotid artery profiles, highlighting the importance of carotid artery examinations. Notably, the SSE%-B2 was independently associated with CIMT; the SSE%-B1 was independently related to the presence of carotid stenosis; the SSE%-B2 and snoring time ratio were independently correlated with the type of carotid artery profile. In contrast, traditional CVD risk factors and OSA parameters were partially related to carotid sonographic measurements in patients with OSA who primarily thought to surgical intervention. Therefore, this non-invasive snoring sound analysis may be a rational approach to stratify the risk of subclinical carotid atherosclerosis and help to prevent possible atherosclerotic CVD events in patients with OSA. Particularly, snoring sound analysis is effective in screening at-risk OSA patients for carotid artery diseases, who are not yet identified by ultrasound because of their relatively early stage of organic damages in the carotid arteries. Further studies are warranted to confirm the clinical significance of the results.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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