Utility of Acoustic Pharyngometry for the Diagnosis of Obstructive Sleep Apnea

Tetyana Kendzerska[1,2,3], Monica Grewal[4,5], and Clodagh M. Ryan[3,5]

[1]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; [2]Sunnybrook Research Institute, Toronto, Ontario, Canada; [3]University of Toronto, Toronto, Ontario, Canada; [4]Royal College of Physicians and Surgeons Ireland; and [5]Centre for Sleep Health and Research, Toronto General Hospital University Health Network, Toronto, Ontario, Canada

ORCID IDs: 0000-0002-5301-1796 (T.K.); 0000-0002-2372-965X (C.M.R.).

Abstract

Rationale: Owing to resource limitations, the testing of patients for obstructive sleep apnea (OSA) is often delayed. There is a need to accurately triage and expedite testing in those with a high pretest probability of OSA. Acoustic pharyngometry is a simple, noninvasive technique used to assess the upper airway cross-sectional area (UA-XSA), which is known to be reduced in those with OSA.

Objectives: To determine the discriminative ability and predictive value of UA-XSA measurements by acoustic pharyngometry for OSA.

Methods: We conducted a cross-sectional study with a clinical cohort of consecutive adults with suspected OSA who had undergone both polysomnography and acoustic pharyngometry. OSA was defined as an apnea–hypopnea index greater than or equal to 5. Multivariable logistic regression analyses and receiver operating characteristic curves were used.

Measurements and Main Results: The cohort included 576 subjects, 87% of whom had OSA and 64% of whom were men. The subjects' median body mass index (BMI) was 30.3 kg/m^2, and their median age was 57 years. The median UA-XSA at FRC when sitting was significantly smaller in those with OSA compared with those without OSA (3.3 cm^2 [interquartile range, 2.7–3.8] vs. 3.7 cm^2 [interquartile range, of 2.9–4.2]). When the analysis was controlled for age, sex, BMI, and comorbidities, the odds of OSA increased for every 1-cm^2 decrease in the mean UA-XSA FRC when sitting (odds ratio, 1.62; 95% confidence interval, 1.23–2.13). The mean UA-XSA provided fair discrimination for OSA (area under the curve, 0.60). A cutoff value of 3.75 cm^2, the point with the best sum of sensitivity and specificity, had sensitivity of 73% and specificity of 46%. The magnitude of the incremental discriminative value of UA-XSA over clinical variables (age, sex, BMI, and comorbidities) was small and nonsignificant ($P = 0.5$).

Conclusions: The mean UA-XSA at FRC when sitting or supine provided no further significant advantage over clinical variables for the discernment of OSA.

Keywords: obstructive sleep apnea; acoustic pharyngometry; screening

(Received in original form January 19, 2016; accepted in final form August 10, 2016)

Author Contributions: All authors made substantial contributions to the literature search, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and provided final approval of the manuscript version to be published. C.M.R. and T.K.: made substantial contributions to the analysis and interpretation of data, as well as drafted the submitted manuscript and revised it critically for important intellectual content; C.M.R.: made substantial contributions to the study's conception and design, obtained research ethics board approval, had full access to all the data in the study, and takes responsibility for the integrity of the data; T.K.: had access to the anonymized data used in this study and takes responsibility for the accuracy of the data analysis; and M.G.: performed data extraction, data entry and data quality checks, and revised the manuscript critically for important intellectual content.

Correspondence and requests for reprints should be addressed to Clodagh M. Ryan, M.B., M.D., Centre for Sleep Health and Research, Toronto General Hospital, 9N-967, 585 University Avenue, Toronto, ON, M5G 2N2 Canada. E-mail: clodagh.ryan@uhn.ca

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 13, No 11, pp 2019–2026, Nov 2016

DOI: 10.1513/AnnalsATS.201601-056OC
Internet address: www.atsjournals.org

Obstructive sleep apnea (OSA) is highly prevalent in the general population (1), with an estimated 80% of OSA being undiagnosed (2, 3). Identification and treatment of severe OSA may be important to modify long-term cardiovascular and cerebrovascular adverse outcomes (4–6) and to improve health-related quality of life (7–9). In many countries, resource limitations contribute to significant delays in the testing of patients for OSA with standard polysomnography (PSG) (10).

Expedited testing for OSA with PSG or polygraphy would be possible if accurate stratification of patients into high pretest probability groups were feasible. However, accurate determination of the pretest probability for OSA has proven challenging, and the performance of many clinical prediction tools has been underwhelming (11, 12).

Acoustic pharyngometry is a noninvasive, cheap, and simple technique used to assess upper airway cross-sectional area (UA-XSA). This technique has been validated previously for subjects with and without OSA in the seated and supine positions (13–16). While OSA is due to the complex interplay of neuromuscular anatomic factors and ventilator instability, previous studies have highlighted the importance of UA geometry in OSA pathogenesis (17).

Acoustic pharyngometry evaluates the static airway during the waking state when there is neuromuscular activation, but disregards dynamic and sleep state changes. Notwithstanding the limitations of this technique, studies using acoustic pharyngometry have shown a significant difference in UA-XSA measurements in individuals with and without OSA, suggesting great potential for this technique in screening for OSA (16, 18). Current evidence for acoustic pharyngometry is inadequate, and published studies are limited by small sample sizes and analytical approaches used (16, 18). We hypothesized that acoustic pharyngometry would serve to play a role in screening for OSA.

Therefore, the objectives of our study were to determine the discriminative ability and predictive value of UA-XSA measurements for OSA in a large clinical population of individuals referred with suspected OSA. Some of the results of this study were presented previously in the form of a poster (19, 20).

Methods

Study Design and Population

We conducted a cross-sectional study with a clinical cohort of consecutive adults with untreated, suspected OSA who had undergone both level 1 full diagnostic PSG and acoustic pharyngometry between July 2009 and January 2014 at the University Health Network, Toronto, Ontario, Canada. Subjects with central sleep apnea and poor-quality acoustic pharyngometry tracings were excluded. A poor-quality acoustic pharyngometry tracing was defined as per the protocol as a tracing that was poorly reproducible with a coefficient of variation greater than 10%. The exclusion criteria for the performance of acoustic pharyngometry included previous oropharyngeal (OP) surgery, intubation within the previous 6 months, severe lung disease requiring supplemental oxygen, and known neuromuscular disease or neurological disease with facial paresis or OP dysphagia or dyskinesia. Information on demographic characteristics (age, sex, race, body mass index [BMI]), level of daytime sleepiness as measured using the Epworth Sleepiness Scale (ESS) score, and prior comorbidities was also collected. Ethical approval was obtained from the University Health Network Research Ethics Board (14-8019-BE).

Polysomnography

Subjects underwent overnight PSG at the University Health Network. Standard techniques and scoring criteria were used to evaluate subjects for sleep stages and arousal from sleep. OSA was diagnosed if the total apnea–hypopnea index (AHI) was greater than or equal to 5 on the basis of PSG. Central and obstructive apnea and hypopnea were defined according to the American Academy of Sleep Medicine guidelines (21). Apnea scoring required a greater than 90% signal drop for at least 10 seconds, and hypopnea scoring required a greater than 50% reduction in nasal pressure signal excursions from baseline and an associated greater than 3% desaturation and/or arousal (21). The scoring criteria were consistent over time. For secondary analyses, other thresholds were also considered to define the presence of OSA: (*1*) AHI greater than or equal to 15, (*2*) AHI greater than 30, and (*3*) different thresholds based on AHI in association with the presence of excessive daytime sleepiness (ESS score, $\geqslant$10).

Acoustic Pharyngometry

The UA-XSA was determined using acoustic pharyngometry (Eccovision; E. Benson Hood Laboratories, Pembroke, MA) (13–15) with subjects in two body positions: (*1*) supine with their heads in the neutral position and (*2*) sitting on a straight-backed chair with head support while awake. The device was positioned in the mouth using a mouthpiece designed to secure the tongue in place. Data were collected between 13:00 and 15:30 and analyzed by a trained technician as previously described (22).

UA-XSA was determined as the mean and minimum areas between the nasal and OP junction (velum) and the glottis as previously described (13). The mean and minimum of three consecutive measurements were used with a coefficient of variation of less than 10% for each study. UA-XSA was measured at the end of passive expiration (at FRC), at maximal inflation (at total lung capacity [TLC]), and at maximal exhalation (at residual volume [RV]).

Analyses

Descriptive statistics were calculated to characterize the entire sample and subgroups by the presence of OSA and by sex. Spearman's rho correlations between UA-XSA measurements and OSA severity measurements (total AHI, supine and nonsupine AHI, REM and non–REM AHI, mean Sa_{O_2}, minimum Sa_{O_2}, and ESS score) were calculated. Characteristics of individuals who were diagnosed with OSA versus those who were not were compared using Student's *t* test for continuous variables for normally distributed data (Wilcoxon's signed-rank test for nonnormally distributed data) or the chi-square test for categorical variables.

Main analyses. For the main analyses, multivariable logistic regression was used to investigate the relationship between the mean UA-XSA at FRC and the diagnosis of OSA. The results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs) indicating change in the odds of the presence of OSA per 1-cm^2 change in the UA-XSA. Additional covariates included were the subject's age in years, sex, and comorbidities (hypertension, heart disease, kidney disease, lung disease, and diabetes). Variables were entered into the statistical model using stepwise regression (23). The estimates derived from the logistic regressions were used also to calculate predicted probabilities at specific values of a key predictor when other covariates remained the same (e.g., sex, age, and comorbidities). To evaluate the performance of our statistical models, we used overall measures such as R^2 and discrimination statistics such as the C-statistic (24). The slope shrinkage factor was estimated on the basis of the model fit as (LR$-df$)/LR, where LR is the likelihood

ratio; values of at least 0.90 were considered acceptable and indicated no evidence of overfitting (24). The Hosmer-Lemeshow test was used to determine the goodness of fit of the logistic regression.

We used receiver operating characteristic (ROC) curves to evaluate the ability of the mean UA-XSA at FRC to discriminate those subjects who were from those who were not diagnosed with OSA. Predefined rules to assess the classification performance according to the area under the ROC curve (AUC) values were applied: AUC of 0.5, no good classification; $0.5 < AUC < 0.6$, poor classification; $0.6 \leq AUC < 0.7$, fair classification; $0.7 \leq AUC < 0.8$, acceptable classification; $0.8 \leq AUC < 0.9$, excellent classification; and AUC greater than or equal to 0.9, outstanding classification (25). The mean UA-XSA values that provided optimal discrimination on the basis of the sum of sensitivity and specificity were determined. To quantify improvement in discrimination ability associated with the UA-XSA, the AUC, R^2, and model fit were compared between models with and without the UA-XSA included as a predictor. The ROC curves were compared using DeLong's test for correlated ROC curves (26). An LR test was used to compare the fit of two models. Given sex- and ethnicity-related differences in upper airway anatomy (27, 28), we tested the predictive and discriminative ability of the mean UA-XSA at FRC separately for men and women as well as for white race.

Secondary analyses. For the secondary analyses, the predictive and discriminative ability of the minimum UA-XSA at FRC and the utility of the mean and minimum UA-XSA at TLC and RV were examined. The predictive and discriminative ability of the upper airway length was also examined. OP length was calculated for subjects in the sitting and supine position (OP sit, OP supine) as distance between the glottis and the velum and was corrected by a person's height. We also explored the predictive and discriminative ability of the UA-XSA using different definitions of OSA as described above, as well as different measures of OSA severity such as REM or supine AHI. Analyses were conducted using R version 2.15.1 software.

Power Calculation

Given that the goal of our study was to determine whether the diagnostic test (different measures of the UA-XSA) has any ability to discriminate patients with OSA from control subjects, we based our power estimation on a hypothesis about whether the AUC exceeds 0.5. With the number of cases at 500, the number of controls at 76, and the type I error rate at 0.05, our study was reasonably powered ($\beta \geq 0.80$) to assess diagnostic tests with an AUC greater than or equal to 0.60 (i.e., to reject the null hypothesis that AUC = 0.5; *see* Equations 2 and 3 in Obuchowski and colleagues [29]).

Results

Subjects

During the study period, 662 subjects underwent acoustic pharyngometry. Of these subjects 36 were excluded because of the presence of treated OSA, 33 because of the absence of PSG performed at the University Health Network, 1 subject because of central sleep apnea, and 16 subjects because of poor-quality acoustic pharyngometric tracings. Among the 576 subjects included, 500 (87%) had OSA (AHI, ⩾5). Acoustic pharyngometry was performed within 35 days (interquartile range [IQR], 39 d) of the diagnostic PSG. Participants were predominantly middle-aged, obese men with a moderate degree of OSA (Table 1). A significant proportion of the subjects had medical comorbidities, but did not have excessive daytime sleepiness as measured using the ESS.

Larger upper airways were observed in men than in women. A statistically significant difference was observed in mean UA-XSA at FRC in any position (Table 1). Significantly larger reductions in UA-XSA with the supine posture occurred in men than in women (Table 1). In addition, significantly ($P < 0.01$) larger UA-XSA was observed in elderly subjects than in their younger counterpart (mean UA-XSA at FRC when sitting was 3.5 cm^2 in

Table 1. Characteristics of clinical cohort: total sample and by sex

Characteristics	Total Sample (*n* = 576)	Women (*n* = 207)	Men (*n* = 369)
Demographics			
Age, yr	57.0 (48.0–65.0)	58.0 (48.0–65.0)	56.0 (47.0–65.0)
Male sex, n (%)	369 (64)	—	—
BMI, kg/m^2	30.3 (26.8–34.7)	31.4 (27.2–37.2)	29.9 (26.8–33.8)
White race, n (%)	502 (87)	182 (88)	320 (87)
Symptoms			
ESS score	7.0 (4.0–10.0)	7.0 (4.0–11.3)	7.0 (4.0–10.0)
Polysomnography			
AHI, events/h	21.0 (9.8–40.1)	14.9 (7.1–31.4)	25.5 (11.2–45.5)
AHI ⩾5, n (%)	500 (87)	171 (83)	329 (89)
AHI ⩾15, n (%)	354 (61)	102 (49)	252 (68)
AHI >30, n (%)	211 (37)	54 (26)	157 (43)
Sleep efficiency, %	77.8 (65.0– 87.2)	78.9 (67.1–87.1)	77.0 (64.3–87.2)
N1, %	8.6 (4.9–14.5)	6.9 (4.2–12.7)	9.8 (5.7–15.9)
N2, %	59.2 (50.9–67.6)	56.5 (48.4–66.9)	60.3 (53.8–68.2)
N3, %	14.2 (5.5–22.3)	19.7 (10.6–28.4)	12.4 (3.1–19.4)
REM, % (missing = 1)	14.3 (9.05–18.8)	13.9 (8.3–18.5)	14.6 (9.3–19.0)
Mean Sa_{O_2}, %	94.4 (93.0–95.8)	94.6 (93.3–96.2)	94.4 (92.9–95.7)
Minimum Sa_{O_2}, %	84.0 (78.0–89.0)	85.0 (78.5–89.0)	84.0 (78.0–88.6)
Comorbidities			
Heart disease, n (%)	232 (40.3)	69 (33.3)	163 (44.2)
HTN, n (%)	278 (48)	102 (49)	176 (48)
Lung disease, n (%)	84 (15)	28 (14)	56 (15)
Kidney disease, n (%)	53 (9)	24 (12)	29 (8)
Diabetes, n (%)	92 (16)	37 (18)	55 (15)
Mean UA-XSA at FRC, cm^2			
Sitting (missing n = 2)	3.3 (2.7–3.9)	2.9 (2.4–3.5)	3.5 (2.9–4.1)*
Supine (missing n = 16)	2.4 (2.1–2.9)	2.3 (2.0–2.8)	2.5 (2.1–3.0)*
Change (missing n = 18)	0.8 (0.4–1.3)	0.5 (0.2–1.0)	0.9 (0.5–1.4)*

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; HTN = hypertension; N1 = Stage N1 sleep; N2 = Stage N2 sleep; N3 = Stage N3 sleep; REM = rapid eye movement sleep; UA-XSA = upper airway cross-sectional area.
Data are presented as median (interquartile range) or number (percent).
*$P < 0.01$ as compared with women for mean UA-XSA.

individuals older than 55 years of age vs. 3.2 cm^2 in those aged 55 years and younger). Compared with subjects without OSA, the mean UA-XSA at FRC when sitting was significantly smaller in those without OSA: 3.3 cm^2 (IQR, 2.7–3.8) and 3.7 cm^2 (IQR, 2.9–4.2), respectively (Table 2). Subjects with OSA were predominantly men with a higher BMI and a higher prevalence of hypertension, diabetes, and heart and kidney disease.

Although some correlations between UA-XSA measurements and PSG variables were statistically significant ($P < 0.05$) and stronger between the UA-XSA measurements and REM or supine AHI than the total AHI, the magnitude of the correlations did not exceed 0.2, indicating weak or no correlation (Figure E1 in the online supplement). Spearman's correlation coefficients between UA-XSA measurements and total AHI, supine AHI, and REM AHI ranged from 0.05– to 0.08, indicating no association.

Prediction of OSA

Logistic regression approach. The odds of OSA significantly increased for every 1-cm^2 decrease in the mean UA-XSA at FRC when sitting (OR, 1.62; 95% CI, 1.23–2.13) when the analysis was controlled for age, sex, BMI, and comorbidities (Table 3). In women, a 1-cm^2 lower mean UA-XSA at FRC when sitting (e.g., 2.5 cm^2 vs. 3.5 cm^2) was associated with a 90% increase in the odds of OSA or a 16% increase in predicted probability of OSA when other covariates remained the same. In men, a 1-cm^2 lower mean UA-XSA at FRC when sitting (e.g., 3 cm^2 vs. 4 cm^2) was associated with a 54% increase in the odds of OSA or an 11% increase in predicted probability of OSA when other covariates remained the same. The C-index for the models selected in stepwise regression (Table 3) ranged from 0.75 (in men) to 0.86 (in women), indicating a good predictive ability (24). The R^2 for the models ranged from 0.18 (in men) to 0.41 (in women), indicating that our models explained from 18 to 41% of the response variable variation with no evidence of overfit based on the slope shrinkage factor.

Receiver operating characteristic curve approach. Poor to fair discriminative ability was observed for different cutpoints of the mean UA-XSA (Table 4). A cutoff value for the mean UA-XSA of 3.75 cm^2 at FRC when sitting provided fair discrimination for OSA (sensitivity, 73%; specificity, 46%; AUC, 0.60). For the mean UA-XSA of 2.7 cm^2 at FRC when sitting (25th percentile), sensitivity was 24% (95% CI, 20–28%) and specificity was 82% (95% CI, 72–89%). The mean UA-XSA at FRC for either sex when supine was not superior to that while sitting. However, the cutoff value for the mean UA-XSA at FRC when sitting and supine differed significantly between sexes, although the discriminative ability was similar (Table 4). In women, for the mean UA-XSA of 2.4 cm^2 at FRC when sitting (25th percentile), sensitivity was 22% (95% CI, 15–28%) and specificity was 89% (95% CI, 78–97%). In men, for the mean UA-XSA of 2.9 cm^2 at FRC when sitting (25th percentile), sensitivity was 23% (95% CI, 19–28%) and specificity was 85% (95% CI, 73–95%).

The discriminative ability of the model that included the mean UA-XSA at FRC when sitting, age, sex, BMI, and heart, kidney, and lung disease were significantly better ($P < 0.0001$) than the mean UA-XSA alone (AUCs, 0.8 vs. 0.6) (Figure 1). No significant improvement in discriminatory ability was observed when UA-XSA FRC when sitting was added to clinical variables ($P = 0.5$): AUC of 0.80 (95% CI, 0.74–0.85) versus 0.79 (95% CI, 0.73–0.84) for the clinical factors only (Figure E1 and Table 1). The magnitude of the incremental predictive value of the UA-XSA over clinical variables as measured by R^2 was very small and insignificant (Table E1); however, additionally including the UA-XSA into the statistical model significantly improved the model fit ($P < 0.001$).

Secondary Analyses

Varying the AHI cutoff threshold to define OSA or analyzing the mean and minimum UA-XSA at RV and TLC did not yield better predictive or discriminative ability (Tables E2–E4). A significant association in

Table 2. Clinical characteristics in cohort with and without obstructive sleep apnea

Characteristics	OSA (*n = 500*)	No OSA (*n = 76*)	*P* Value
Demographics			
Age, yr	48.0 (39.0–57.5)	47.5 (31.8–62.0)	<0.0001
Male sex, n	329 (66)	40 (53)	0.04
BMI, kg/m^2	31.1 (27.5–35.3)	27.0 (24.2–31.2)	<0.0001
Symptoms			
ESS	7 (4–10)	6 (3–12)	0.79
Polysomnography			
Sleep efficiency, %	77.6 (64.4–86.9)	78.8 (69.8–88.7)	0.26
N1, %	9.0 (5.1–14.9)	6.2 (3.8–13.0)	0.01
N2, %	59.4 (50.8–68.1)	57.7 (51.8–63.6)	0.20
N3, %	13.6 (5.2–22.0)	18.1 (11.8–24.1)	0.01
REM, %	14.2 (9.3–18.7)	15.1 (8.2–20.4)	0.28
AHI, events/h	25.0 (13.7–43.3)	2.3 (1.0–3.4)	<0.0001
Mean Sa_{O_2}, %	94.2 (92.8–95.5)	94.4 (96.2–97.1)	<0.0001
Comorbidities			
Hypertension, n (%)	257 (51)	21 (28)	0.0002
Heart disease, n (%)	216 (43)	16 (21)	0.0004
Lung disease, n (%)	71 (14)	13 (17)	0.62
Kidney disease, n (%)	52 (10)	1 (1)	0.02
Diabetes, n (%)	87 (17)	5 (7)	0.03
UA-XSA area at FRC, cm^2			
Mean			
Sitting	3.3 (2.7–3.8)	3.7 (2.9–4.2)	0.006
Supine	2.4 (2.1–2.9)	2.7 (2.1–2.9)	0.17
Change	0.8 (0.4–1.3)	0.9 (0.5–1.6)	0.06
Minimum			
Sitting	2.0 (1.6–2.5)	2.1 (1.8–2.6)	0.09
Supine	1.6 (1.3–1.9)	1.7 (1.3–1.9)	0.33
Change	0.45 (0.06–0.81)	0.47 (0.04–1.05)	0.35

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; N1 = Stage N1 sleep; N2 = Stage N2 sleep; N3 = Stage N3 sleep; REM = rapid eye movement sleep; OSA = obstructive sleep apnea; UA-XSA = upper airway cross-sectional area. Data are presented as median (interquartile range) or number (percent).

Table 3. Results of multivariable logistic regression analyses

	Odds Ratio (95% Confidence Interval)			
	Total Sample*	**Women†**	**Men‡**	**White Race***
Sitting				
Per 1-cm^2 decrease in UA-XSA	1.62 (1.23–2.13)	1.90 (1.11–3.25)	1.54 (1.10–2.15)	1.53 (1.14–2.05)
C-index	0.80	0.86	0.75	0.81
R^2	0.27	0.41	0.18	0.29
Slope SF§	0.92	0.93	0.85	0.92
Supine				
Per 1-cm^2 decrease in UA-XSA	1.14 (0.75–1.74)	1.55 (0.73–3.31)	0.98 (0.57–1.66)	1.12 (0.71–1.76)
C-index	0.80	0.86	0.75	0.81
R^2	0.26	0.44	0.15	0.29
Slope SF§	0.917	0.94	0.82	0.92
Change				
Per 1-cm^2 decrease in UA-XSA	1.87 (1.31–2.66)	1.56 (0.75–3.25)	1.91 (1.27–2.87)	1.70 (1.17–2.49)
C-index	0.81	0.87	0.77	0.82
R^2	0.29	0.44	0.20	0.32
Slope SF§	0.927	0.94	0.87	0.92

Definition of abbreviations: SF = shrinkage factor; UA-XSA = upper airway cross-sectional area.
The data show an association between the upper airway cross-sectional area at FRC and the presence of obstructive sleep apnea when the analysis was controlled for age, sex, and comorbidities.
*Statistical model for the total sample and white race, based on stepwise regression: UA-XSA; age; body mass index (BMI); sex; and heart, kidney, and lung diseases.
†Statistical model in women: UA-XSA, age, BMI, and kidney disease.
‡Statistical model in men: UA-XSA, age, BMI, and heart and lung disease.
§The slope shrinkage factor was estimated from the model fit as (LR−*df*)/LR, where LR is the likelihood ratio; values of at least 0.90 were considered acceptable and indicate no evidence of overfitting.

the univariate logistic regression model was observed only between OP seated and the presence of OSA ($P = 0.02$). When primary analyses were replicated, this measurement did not show better discriminative ability (AUCs ranged from 0.51 to 0.58).

Discussion

To our knowledge, this is the largest study to date performed in a clinical population of consecutive patients with suspected OSA to examine the predictive and discriminative ability of the UA-XSA measured using acoustic pharyngometry. This study demonstrates that the mean UA-XSA at FRC when sitting was a significant predictor of OSA when we controlled for important confounders. However, it also demonstrates that the discriminant validity was only fair for identifying those with OSA.

Consistent with other studies, we found that the UA-XSA measurements were significantly associated with the presence of OSA when we controlled for confounders using logistic regression in a clinical cohort of patients with suspected OSA and multiple comorbidities (16, 18). Yet, using an ROC approach, we found that the discriminative ability of the UA-XSA measurements was only fair. Only one other study, performed by DeYoung and colleagues, used this approach (18). Specifically, the reported AUC for the minimal cross-sectional area predicting an AHI less than 15 per hour in their study was 0.85, which was considerably higher than in our study. The observed difference between DeYoung's study and our study may be explained by their smaller cohort (60 vs. 576 subjects), data collected from clinical and community samples (51 and 9, respectively) versus data collected from a clinical cohort only, disparate distribution of cases as compared with our study (OSA vs. controls, 1:1 vs.

Table 4. Results of receiver operating characteristic curve analyses

	Best* Threshold	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**AUC† (95% CI)**
Entire sample				
Sitting	3.75 cm^2	0.46 (0.34–0.57)	0.73 (0.69–0.77)	0.60 (0.53–0.67)
Supine	2.65 cm^2	0.52 (0.41–0.63)	0.66 (0.62–0.70)	0.55 (0.48–0.62)
Change	1.45 cm^2	0.31 (0.20–0.41)	0.82 (0.79–0.86)	0.57 (0.50–0.64)
Women				
Sitting	3.75 cm^2	0.39 (0.25–0.56)	0.88 (0.84–0.92)	0.66 (0.56–0.76)
Supine	2.65 cm^2	0.51 (0.34–0.69)	0.73 (0.66–0.80)	0.60 (0.49–0.70)
Change	0.35 cm^2	0.83 (0.69–0.94)	0.35 (0.27–0.43)	0.60 (0.50–0.71)
Men				
Sitting	4.55 cm^2	0.33 (0.18–0.48)	0.86 (0.82–0.90)	0.60 (0.50–0.69)
Supine	2.65 cm^2	0.53 (0.38–0.68)	0.63 (0.57–0.68)	0.53 (0.44–0.63)
Change	1.55 cm^2	0.40 (0.25–0.55)	0.80 (0.76–0.84)	0.59 (0.49–0.69)

Definition of abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval.
Data represent the AUC as well as the specificity and sensitivity of optimal cutpoints for discriminating patients with versus without obstructive sleep apnea using the mean upper airway cross-sectional area at FRC.
*"Best" means the point with the best sum of sensitivity and specificity.
†Based on DeLong's test (26).

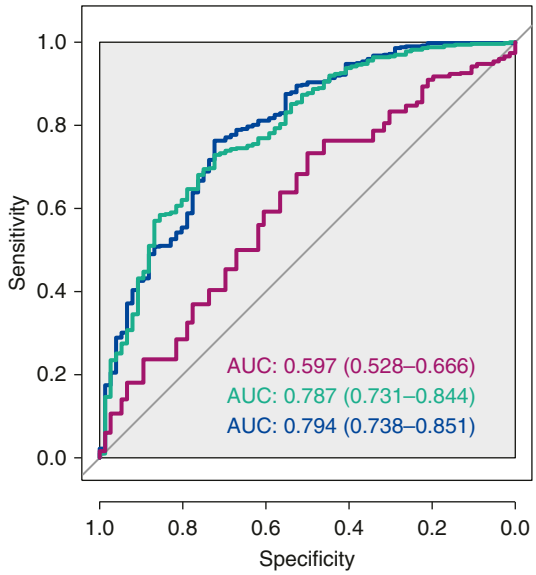

Figure 1. Results of receiver operating characteristic curve analyses: ability of clinical factors alone (*green line*), upper airway cross-sectional area alone (*purple line*), and these measurements in combination with clinical factors (*blue line*) to discriminate individuals with from those without a diagnosis of obstructive sleep apnea (apnea–hypopnea index ⩾5). The clinical factors studied were age; body mass index; sex; and prior heart, kidney, and lung disease AUC = area under the receiver operating characteristic curve.

6.6:1), and the failure to consider race as a confounder (30).

Importantly, our results highlight the limitations of the use of the OR, a single measure of association, as an effective tool for classifying persons (31). While investigating the relationship between an OR and ROC curves, it has been illustrated that a predictor with an OR of 3 or greater may in fact be a very poor classification tool. The ROC curve approach has been recommended as one of the appropriate classification tools, given that it does not depend on the units in which the predictor was measured (e.g., as we reported above, OR per 1-cm^2 decrease). Moreover, ROC curves provide a natural common scale for comparing different markers even when they are measured in completely different units. Using ROC curves, the UA-XSA had only poor to fair discriminant value, which was significantly improved as measured by the AUC from 0.6 to 0.8 by the addition of age, sex, BMI, and comorbidities to the model. The added discriminatory value of knowing UA-XSA beyond the clinical information was small and nonsignificant. This suggests that, despite the magnitude of the effect the UA-XSA (as measured by OR) being relatively large and significant controlling for confounders, further studies are needed to test the incremental value of the UA-XSA in the predictive model over a range of patient demographics and anthropometric measurements (32). In particular, acoustic pharyngometry may be more predictive in a community sample, but further work is required to develop and validate a predictive model.

In agreement with prior studies, we have shown that the mean UA-XSA in men is larger than in women, that significant reductions in the mean UA-XSA occur from the sitting to the supine position, and that those reductions were greater in men than in women (28.5% vs. 20.7% in our study, respectively) (28, 33). Similarly to other studies, we observed an increase in the UA-XSA with age (34). This may be due to age-related neurogenic and muscular changes to the airway wall or enlargement in UA soft tissues that may impact the mechanical interactions between the UA and extraluminal forces, causing alterations to the UA geometry (32, 34).

Moreover, as shown in previous work, there was a smaller mean UA-XSA at FRC (16, 28) and also a smaller UA-XSA at FRC in the supine position than in the nonsupine position in those with and without OSA, consistent with other studies (16). Similarly to the Brown and colleagues study, no significant differences were observed in the positional change in the mean and minimum UA-XSA between those with and without OSA (35). However, contrary to the studies by Monahan and colleagues and DeYoung and coworkers, we did not demonstrate a significant difference in the minimum UA-XSA at FRC (18, 28). The reason for these differences is uncertain, but our subjects were less obese. As obesity is known to cause greater reductions in pharyngeal size, it may be a factor in the apparent differences between studies (36).

One of the key pathophysiological causes of OSA is the anatomically compromised airway (17, 37). The supine body position is posited to have a strong influence on both the presence and severity of OSA (38) and the UA-XSA (35). However, in our study, evaluation of the UA-XSA at FRC when supine or the change in the UA-XSA upon lying down did not further enhance the ability to predict OSA. This may be due to the greater importance of reductions in FRC in those with supine OSA as a triggering factor for OSA rather than the changes in UA shape or size (39). Furthermore, the pathogenetic mechanisms responsible for OSA are multifactorial, and the activation of pharyngeal dilator muscles during the waking state and the absence of ventilatory instability may explain the fair to poor discriminative ability found in our study. Although, the use of REM AHI rather than total AHI as a surrogate measurement of the atonic airway did not change the predictive and discriminative ability of the UA-XSA measurements considerably.

Strengths and Limitations

Our study has a number of strengths, including the relatively large sample size and our analysis of results based on both sex and race. There are also a number of limitations evident in this study, including the absence of some key anthropometric and physiological variables, such as neck circumference, waist-to-hip ratio, and lung volumes in both the supine and seated positions, that may have improved the predictive ability of our model (39, 40). Moreover, the performance of testing during the waking state may not accurately predict the UA-XSA during sleep, and we did not assess pharyngeal collapsibility, which may be of greater

importance in older subjects with regard to the pathogenesis of OSA (41, 42). Furthermore, our study was conducted in a single academic sleep center with a cohort of subjects with suspected OSA, which may limit its generalizability and make it prone to spectrum bias. The small cohort of subjects with an AHI less than 5 per hour may explain the poorer performance of acoustic pharyngometry in our population. As a community sample has less spectrum bias, this test may perform superiorly in that setting.

Conclusions

As a screening tool, acoustic pharyngometry is performed quickly and easily in awake subjects. Although the mean UA-XSA at FRC when sitting was a significant predictor of OSA when the analysis was controlled for important confounders, it had only fair discriminant validity for identifying those with OSA in a clinical population and had no significantly greater discriminant value than the use of clinical variables. Therefore, it is probably of no clinical utility in this setting. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–1014.
2 Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:136–143.
3 Simpson L, Hillman DR, Cooper MN, Ward KL, Hunter M, Cullen S, James A, Palmer LJ, Mukherjee S, Eastwood P. High prevalence of undiagnosed obstructive sleep apnoea in the general population and methods for screening for representative controls. *Sleep Breath* 2013;17:967–973.
4 Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, *et al*. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6:e1000132.
5 Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034–2041.
6 Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 2005;172:1447–1451.
7 Appleton SL, Vakulin A, McEvoy RD, Vincent A, Martin SA, Grant JF, Taylor AW, Antic NA, Catcheside PG, Wittert GA, *et al*. Undiagnosed obstructive sleep apnea is independently associated with reductions in quality of life in middle-aged, but not elderly men of a population cohort. *Sleep Breath* 2015;19:1309–1316.
8 Iacono Isidoro S, Salvaggio A, Lo Bue A, Romano S, Marrone O, Insalaco G. Quality of life in patients at first time visit for sleep disorders of breathing at a sleep centre. *Health Qual Life Outcomes* 2013;11:207.
9 Naismith S, Winter V, Gotsopoulos H, Hickie I, Cistulli P. Neurobehavioral functioning in obstructive sleep apnea: differential effects of sleep quality, hypoxemia and subjective sleepiness. *J Clin Exp Neuropsychol* 2004;26:43–54.
10 Rotenberg B, George C, Sullivan K, Wong E. Wait times for sleep apnea care in Ontario: a multidisciplinary assessment. *Can Respir J* 2010; 17:170–174.
11 Moro M, Westover MB, Kelly J, Bianchi MT. Decision modeling in sleep apnea: the critical roles of pretest probability, cost of untreated obstructive sleep apnea, and time horizon. *J Clin Sleep Med* 2016; 12:409–418.
12 Pataka A, Daskalopoulou E, Kalamaras G, Fekete Passa K, Argyropoulou P. Evaluation of five different questionnaires for assessing sleep apnea syndrome in a sleep clinic. *Sleep Med* 2014; 15:776–781.
13 Kamal I. Normal standard curve for acoustic pharyngometry. *Otolaryngol Head Neck Surg* 2001;124:323–330.
14 Kamal I. Test-retest validity of acoustic pharyngometry measurements. *Otolaryngol Head Neck Surg* 2004;130:223–228.
15 Kamal I. Acoustic pharyngometry patterns of snoring and obstructive sleep apnea patients. *Otolaryngol Head Neck Surg* 2004;130:58–66.
16 Jung DG, Cho HY, Grunstein RR, Yee B. Predictive value of Kushida index and acoustic pharyngometry for the evaluation of upper airway in subjects with or without obstructive sleep apnea. *J Korean Med Sci* 2004;19:662–667.
17 Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea: identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188:996–1004.
18 Deyoung PN, Bakker JP, Sands SA, Batool-Anwar S, Connolly JG, Butler JP, Malhotra A. Acoustic pharyngometry measurement of minimal cross-sectional airway area is a significant independent predictor of moderate-to-severe obstructive sleep apnea. *J Clin Sleep Med* 2013;9:1161–1164.
19 Kendzerska T, Grewal M, Ryan CM. Utility of acoustic pharyngometry in the diagnosis of obstructive sleep apnea. Poster presented at the Seventh Annual Canadian Sleep Society Conference. September 27, 2015, Toronto, ON, Canada. Poster P7.
20 Kendzerska T, Grewal M, Ryan CM. Utility of acoustic pharyngometry in the diagnosis of obstructive sleep apnea. *Am J Respir Crit Care Med* 2016;193:A5976.
21 Berry RB, Gamaldo CE, Harding SM, Marcus CL, Vaughn BV; American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2. Darien, IL: American Academy of Sleep Medicine; 2012.
22 Shiota S, Ryan CM, Chiu KL, Ruttanaumpawan P, Haight J, Arzt M, Floras JS, Chan C, Bradley TD. Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects. *Thorax* 2007;62:868–872.
23 Venables WN, Ripley BD. Generalized linear model. In: Modern applied statistics with S, 4th ed. New York: Springer; 2002. p. 183–210.
24 Harrell FE. RMS: regression modeling strategies, R package version 4.0-0. 2013.
25 Hosmer DW, Lemeshow S. Assessing the fit of the model. In: Applied logistic regression. Wiley series in probability and statistics, 2nd ed. New York: Wiley; 2000. p. 143–202.
26 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–845.
27 Segal Y, Malhotra A, Pillar G. Upper airway length may be associated with the severity of obstructive sleep apnea syndrome. *Sleep Breath* 2008;12:311–316.
28 Monahan K, Kirchner HL, Redline S. Oropharyngeal dimensions in adults: effect of ethnicity, gender, and sleep apnea. *J Clin Sleep Med* 2005;1:257–263.
29 Obuchowski NA, Lieber ML, Wians FH Jr. ROC curves in clinical chemistry: uses, misuses, and possible solutions. *Clin Chem* 2004; 50:1118–1125.
30 Patel SR, Frame JM, Larkin EK, Redline S. Heritability of upper airway dimensions derived using acoustic pharyngometry. *Eur Respir J* 2008;32:1304–1308.
31 Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am J Epidemiol* 2004;159:882–890.
32 Strohl KP, Butler JP, Malhotra A. Mechanical properties of the upper airway. *Compr Physiol* 2012;2:1853–1872.
33 Martin SE, Mathur R, Marshall I, Douglas NJ. The effect of age, sex, obesity and posture on upper airway size. *Eur Respir J* 1997;10:2087–2090.
34 Carlisle T, Carthy ER, Glasser M, Drivas P, McMillan A, Cowie MR, Simonds AK, Morrell MJ. Upper airway factors that protect against obstructive sleep apnoea in healthy older males. *Eur Respir J* 2014; 44:685–693.

35 Brown IB, McClean PA, Boucher R, Zamel N, Hoffstein V. Changes in pharyngeal cross-sectional area with posture and application of continuous positive airway pressure in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1987;136: 628–632.
36 Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1984;130:175–178.
37 Ryan CM, Bradley TD. Pathogenesis of obstructive sleep apnea. *J Appl Physiol (1985)* 2005;99:2440–2450.
38 Sunnergren O, Broström A, Svanborg E. Positional sensitivity as a confounder in diagnosis of severity of obstructive sleep apnea. *Sleep Breath* 2013;17:173–179.
39 Joosten SA, Sands SA, Edwards BA, Hamza K, Turton A, Lau KK, Crossett M, Berger PJ, Hamilton GS. Evaluation of the role of lung volume and airway size and shape in supine-predominant obstructive sleep apnoea patients. *Respirology* 2015;20:819–827.
40 Owens RL, Malhotra A, Eckert DJ, White DP, Jordan AS. The influence of end-expiratory lung volume on measurements of pharyngeal collapsibility. *J Appl Physiol (1985)* 2010;108:445–451.
41 Eikermann M, Jordan AS, Chamberlin NL, Gautam S, Wellman A, Lo YL, White DP, Malhotra A. The influence of aging on pharyngeal collapsibility during sleep. *Chest* 2007;131:1702–1709.
42 Malhotra A, Pillar G, Fogel R, Beauregard J, Edwards J, White DP. Upper-airway collapsibility: measurements and sleep effects. *Chest* 2001;120:156–161.