Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects

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Isono, Shiroh, John E Remmers, Atsuko Tanaka, Yasuhide Sho, Jiro Sato, and Takashi Nishino. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. *J. Appl. Physiol.* 82(4): 1319–1326, 1997.— Anatomic abnormalities of the pharynx are thought to play a role in the pathogenesis of obstructive sleep apnea (OSA), but their contribution has never been conclusively proven. The present study tested this anatomic hypothesis by comparing the mechanics of the paralyzed pharynx in OSA patients and in normal subjects. According to evaluation of sleep-disordered breathing (SDB) by nocturnal oximetry, subjects were divided into three groups: normal group ($n = 17$), SDB-1 ($n = 18$), and SDB-2 ($n = 22$). The static pressure-area relationship of the passive pharynx was quantified under general anesthesia with complete paralysis. Age and body mass index were matched among the three groups. The site of the primary closure was the velopharynx in 49 subjects and the oropharynx in only 8 subjects. Distribution of the location of the primary closure did not differ among the groups. Closing pressure (P_C) of the velopharynx for SDB-1 and SDB-2 groups (0.90 ± 1.34 and 2.78 ± 2.78 cmH$_2$O, respectively) was significantly higher than that for the normal group (-3.77 ± 3.44 cmH$_2$O; $P < 0.01$). Maximal velopharyngeal area for the normal group (2.10 ± 0.85 cm^2) was significantly greater than for SDB-1 and SDB-2 groups (1.15 ± 0.46 and 1.06 ± 0.75 cm^2, respectively). The shape of the pressure-area curve for the velopharynx differed between normal subjects and patients with SDB, being steeper in slope near P_C in patients with SDB. Multivariate analysis of mechanical parameters and oxygen desaturation index (ODI) revealed that velopharyngeal P_C was the only variable highly correlated with ODI. Velopharyngeal P_C was associated with oropharyngeal P_C, suggesting mechanical interdependence of these segments. We conclude that the passive pharynx is more narrow and collapsible in sleep-apneic patients than in matched controls and that velopharyngeal P_C is the principal correlate of the frequency of nocturnal desaturations.

static pressure-area relationship; closing pressure; oxygen desaturation; pharyngeal compliance

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ONE KEY FEATURE OF SLEEP is suppression of upper airway (UA) muscle activity, and a sleep-related decrease in UA dilator muscle force is thought to lead to pharyngeal narrowing or closure in patients with obstructive sleep apnea (OSA) or hypopnea (27). This suggests either that patients with OSA reduce the UA dilator muscle activity more than normal subjects during sleep (neural hypothesis) or that OSA patients experience a normal sleep-related reduction in UA muscle activity that occurs along with a pharynx that is structurally less stable (anatomic hypothesis). Compared with normal subjects, patients with OSA have significantly greater genioglossus muscle activity while awake (24, 39), which may represent a compensatory response to a structurally narrow pharynx. If so, the compensation is incomplete, because apneic subjects have smaller cross-sectional area of the pharynx (2, 14, 20, 28) and higher supraglottic resistance while awake (1). In this way, the active contraction of the UA muscles during wakefulness may, to some extent, mask an underlying anatomic abnormality. Although the anatomic and neural hypotheses for the pathogenesis of OSA are not necessarily contradictory, recent evidence favors the anatomic hypothesis (1, 2, 14, 20, 24, 39). The interaction of the neural and anatomic factors for the maintenance of the UA patency, however, complicates the interpretation of available data because the UA muscle activities were not controlled in these studies. Therefore, the hypothesis has never been critically tested because of methodological difficulty in separating anatomic factors from neural factors. The purpose of the present study was to test the anatomic hypothesis that sleep-apneic subjects have an intrinsically narrowed and collapsible pharynx.

We have previously described a simple method for evaluating anatomic properties of the pharynx independently of neural factors (16). Total muscle paralysis produced by administration of muscular blockade under general anesthesia is used to completely eliminate pharyngeal muscle contraction. Under such circumstances, we evaluated the static mechanical properties of the atonic pharynx by measuring cross-sectional area of the pharynx at various pharyngeal luminal pressures under conditions of no respiratory airflow. The static mechanics of the pharynx is graphically best expressed by plotting the pressure-area relationship, a curve that defines a maximum area, a closing pressure, and a compliance of the pharynx (15). Accordingly, anatomic differences between the OSA patients and the normal subjects should be manifested as differences in these characteristics of the static pressure-area relationship. For instance, if OSA patients have a narrowed and collapsible pharynx, the curve will be below that of normal subjects. We, therefore, compared static pressure-area relationship of the passive pharynx of OSA patients with normal controls matched for age and body mass index (BMI).

METHODS

Subjects

We studied 49 men and 8 women. Thirty-six subjects with OSA were recruited from a group of apneic subjects who chose uvulopalatopharyngoplasty (UPPP) as a treatment for their apnea. All had a history of excessive daytime sleepiness,

habitual snoring, witnessed repetitive apnea, and nocturnal oxygen desaturation evaluated by oximetry. They participated in this study as part of a routine preoperative evaluation of pharyngeal mechanics to determine whether they were favorable candidates for UPPP (21).

To obtain age- and BMI-matched normal controls, we invited to participate in this study 24 patients who were scheduled to have surgery in our hospital for reasons unrelated to OSA. None of them had a history of cardiac and pulmonary disease; three declined to participate. Of the remaining 21 participants, 9 did not snore, 5 snored occasionally but had no historical evidence of breathing disorders during sleep, and 7 were habitual snorers. Careful clinical evaluation of the last subgroup revealed that two patients had a clear history of excessive daytime sleepiness and witnessed repetitive apnea. The aim and potential risks of the study were fully explained to each subject, and informed consent was obtained from each. The investigation was approved by the Hospital Ethics Committee.

Overnight Oximetry and Classification of the Subjects

Sleep-disordered breathing (SDB) was evaluated by a pulse oximeter (Pulsox-5; Minolta, Tokyo, Japan). All subjects were instructed to attach a finger probe of the oximeter before sleep and to remove the probe upon awakening. Digital readings of arterial oxygen saturation (Sa_{O_2}) and pulse rate were stored every 5 s in a memory card. The stored data were displayed on a computer screen to check quality of the recordings. The computer calculated oxygen desaturation index (ODI), which was defined as the number of oxygen desaturation exceeding 4% from the baseline, and the percent of time spent at Sa_{O_2} <90% (CT_{90}).

The overall population was divided into three groups based on the results of the overnight pulse oximetry: *1*) subjects with ODI ≤5/h and CT_{90} = 0 were assigned to a normal group; *2*) subjects with ODI between 5 and 20/h were assigned to a group with mild SDB, referred to as SDB-1; and *3*) subjects with ODI ≥20/h were assigned to a severe SDB group, referred to as SDB-2.

Pharyngeal Endoscopy Under General Anesthesia

Preparation of the subjects. The subjects were initially premedicated with 0.5 mg of atropine. Studies were performed with the subject in a supine position on an operating table and with the neck in a neutral position. The subject wore a modified tight-fitting nasal continuous positive airway pressure (Paw) mask or a modified anesthetic nasal mask. The possibility of air leaks between the mask and the face was carefully examined, particularly when the airway was pressurized to 20 cmH_2O. General anesthesia was induced by intravenous administration of thiopental sodium (4 mg/kg). Intravenous injection of a muscle relaxant (vecuronium 0.2 mg/kg) produced complete paralysis throughout the experiment. Anesthesia was maintained by inhalation of 2–4% sevoflurane in oxygen while the subject was ventilated with positive pressure by using an anesthetic machine. Sa_{O_2}, electrocardiogram, and blood pressure were continuously monitored. Mechanical ventilation was set to maintain normal levels of Sa_{O_2} and blood pressure. A slim endoscope (FB 15H or FB10H, 3-mm and 4.5-mm OD, respectively; Pentax, Tokyo, Japan) was inserted through the nasal mask and a naris. The tip of the scope was positioned to visualize the velopharynx (VP; retropalatal space) or the oropharynx (OP; retroglossal space). A closed-circuit camera (ETV8; Nisco, Saitama, Japan) was connected to the endoscope, and pharyngeal images were recorded on a videotape. The experiment was terminated

with administration of atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg) to reverse muscle paralysis.

Experimental procedure. To determine the pressure-area relationship of the pharynx, the anesthesia machine was disconnected from the nasal mask, which was then connected to a pressure-control system capable of accurately producing a constant, preselected Paw ranging from −20 to 20 cmH_2O in steps of 1 cmH_2O. Cessation of mechanical ventilation resulted in apnea caused by complete muscle paralysis. Paw was immediately increased and maintained at 20 cmH_2O. While the subject remained apneic for 2–3 min, Paw was slowly reduced from 20 cmH_2O to Pc_{VP}, i.e., the pressure at which the VP was seen to close completely. Sa_{O_2} remained >99% throughout this apneic test in all subjects. This procedure of experimentally induced apnea allowed construction of the pressure-area relationship of the visualized pharyngeal segment. Measurements were made for the VP and OP airway, and the distance between the tip of the endoscope and the narrowing site was measured by using a wire passed through an aspiration channel of the endoscope.

Data Analysis

To convert the image on the monitor to an absolute value of cross-sectional area of the pharynx, magnification of the imaging system was estimated for every 1.0-mm distance between the tip of the endoscope and an object in a range of 10–30 mm. At a defined value of Paw, the image of the pharyngeal lumen was outlined on a tracing paper (50 g/m²). The lumen tracing was cut from the paper and weighed (ER120; A & D, Tokyo, Japan). The area of the paper was converted to pharyngeal cross-sectional area according to the distance-magnification relationship. For a constant distance, the area measurements were validated to be accurate within 8% (−0.1 ± 4.6%, range; +6.5 to −7.6%) by known-diameter tubes (4- to 9-mm ID).

The measured luminal cross-sectional area was plotted as a function of Paw. We defined Pc as a pressure corresponding to zero area. At high values of Paw, cross-sectional area became relatively constant and maximum area (A_{max}) was determined as mean values of measured area at highest three Paw values (18, 19, and 20 cmH_2O). As reported previously (15), the pressure-area relationship of each pharyngeal segment was fitted by an exponential function

$$A = A_{max} - B * exp(- K * Paw)$$

where B and K are constants. A nonlinear least square technique was used for the curve fitting, and the quality of the fitting was provided by coefficient R^2 (SigmaPlot version 2.0, Jandel Scientific Software, San Rafael, CA). A regressional estimate of closing pressure (Pc') was calculated from the following equation for each pharyngeal segment

$$Pc' = ln(B/A_{max})/K$$

The shape of the pressure-area relationship was described by the value of K and by the half-dilation pressure (P_{50}), i.e., the pressure above Pc' associated with 0.5 A_{max} [$P_{50} = ln(2)/K$]. P_{50} equals the increment in Paw above Pc' required to distend the pharynx to one-half the A_{max}.

Statistical Analysis

The groups were compared by using a one-way analysis of variance. Post hoc analysis of significant comparisons was performed with Newman-Keuls multiple range test to determine the source of these differences. To determine major contributing factors to nocturnal desaturation, multivariate

linear regression analyses were performed employing Huber's M-estimator (S-plus version 3.2, Mathsoft, Seattle, WA) (42). The models used ODI transformed on a logarithmic scale as the dependent variable to normalize the distribution. Backward stepwise method was initially applied for the following mechanical parameters of each pharyngeal segment: A_{max}, B, K, P_C', and P_{50}. Correlation between the variables was assessed by Pearson correlation coefficients. All values are expressed as means $\pm$ SD. $P < 0.05$ was considered to be significant.

RESULTS

According to our classification criteria, we placed 17 subjects in the normal group, 18 in the SDB-1 group, and 22 in the SDB-2 group. Four patients with SDB were identified from the group of patients having a surgery other than UPPP. Age, height, weight, BMI, ODI, and CT_{90} for each group are presented in Table 1. The anthropometric data did not differ among the groups. The site of the primary closure was the VP in 49 subjects and the OP in 8 subjects. Distribution of the location of the primary closure did not differ amongst the groups (Fig. 1).

P_C and A_{max} for the Three Groups

Box plots of observed P_C for each group are presented in Fig. 1. Mean values of P_C for SDB-1 and SDB-2 groups (0.56 ± 1.54 and 2.23 ± 2.96 cmH$_2$O, respectively) were significantly higher than that of the normal group (-4.35 ± 4.15 cmH$_2$O) but did not differ significantly between the apneic groups. Figure 2 shows A_{max} at the VP (A_{maxVP}) and at the OP (A_{maxOP}) for each group. Mean values of A_{maxVP} of SDB-1 and SDB-2 groups (1.15 ± 0.46 and 1.06 ± 0.75 cm^2, respectively) did not differ significantly, but each was significantly smaller than that of normal group (2.10 ± 0.85 cm^2). Mean A_{maxOP} of the SDB-2 group (2.10 ± 0.91 cm^2) was significantly smaller than those of the normal and SDB-1 group (3.02 ± 1.23 and 3.15 ± 1.21 cm^2, respectively).

Results of Exponential Curve Fitting

Table 2 summarizes the results of the exponential fitting of the pressure-area data for each subject. The R^2 values were uniformly high (± 0.93), indicating that
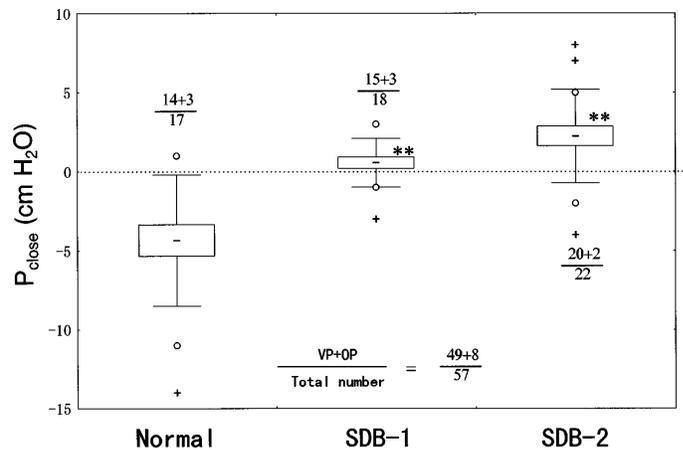

Fig. 1. Box plots illustrating observed closing pressure (P_C). Distribution of sites of primary closure was provided for each of 3 groups: normal, sleep-disordered breathing (SDB)-1, and SDB-2. Mean values are indicated by horizontal bar within each box; bars above and below each box represent SE. End of vertical line denotes SD. ○ or + symbols, outliers. VP, velopharynx; OP, oropharynx. $** P < 0.01$ vs. normal group.

the exponential function fitted the pressure-area data reasonably well for both pharyngeal segments. K values of the normal group were significantly smaller than those for the SDB-1 and SDB-2 groups at the VP and the OP. This indicates that the curves of normal subjects were flatter (i.e., less round) than for SDB-1 and SDB-2 groups.

The pharyngeal pressure-area curves obtained by exponential curve fitting for each subject are presented by group in Fig. 3. As shown in the upper row, P_{VP}-area curves of the normal group lay above those of SDB-1 and SDB-2 groups, having larger calculated A_{maxVP} and lower P_{CVP}'. Overlap of VP curves between the normal subjects and the apneic subjects was minimal. Only two normal subjects had positive P_{CVP}', whereas 33 of 40 patients with SDB had positive values of P_{CVP}'. P_{OP}-area curves of apneic subjects were likely to be below those of normal subjects, although the separation

Table 1. *Age, body size, and nocturnal oximetry data*

	Normal Subjects (ODI $\leqq$ 5, CT$_{90}$ = 0)	SDB-1 (5 < ODI < 20)	SDB-2 (ODI $\geqq$ 20)
No. of subjects (men, women)	17 (14, 3)	18 (15, 3)	22 (20, 2)
Age, yr	42.3 ± 11.9	44.9 ± 10.8	45.6 ± 11.8
Height, m	1.66 ± 0.09	1.66 ± 0.15	1.68 ± 0.05
Weight, kg	75.0 ± 14.7	72.2 ± 15.4	81.1 ± 13.4
BMI, kg/m^2	27.2 ± 4.8	26.5 ± 5.6	28.6 ± 4.3
ODI, %/h	2.6 ± 1.5	$13.7 \pm 3.7^*$	$39.4 \pm 17.2^*\dagger$
CT$_{90}$, %	0 ± 0	$4.1 \pm 7.0^*$	$23.1 \pm 22.2^*\dagger$

Values are means $\pm$ SD. SDB, sleep-disordered breathing; BMI, body mass index; ODI, oxygen desaturation index defined as no. of oxygen desaturations exceeding 4% from baseline; CT$_{90}$, %time spent at oxygen saturation <90%. $* P < 0.01$ vs. normal group; $\dagger P < 0.01$ vs. SDB-1 group.
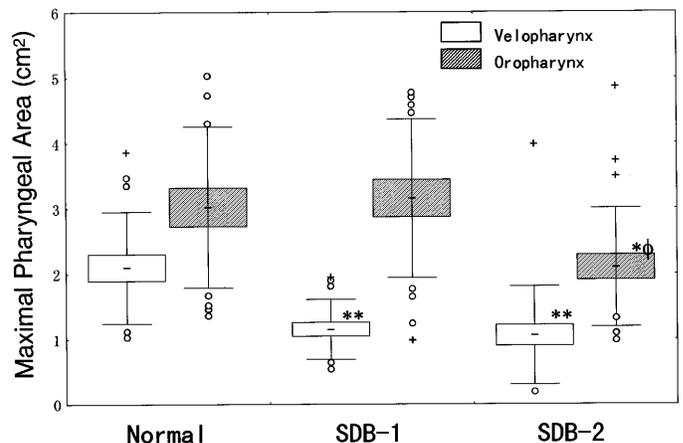

Fig. 2. Box plots showing maximum cross-sectional area of VP and OP for each group. Maximum area (A_{max}) was determined as mean values of measured area at highest 2 airway pressures (Paw; 18, 19, and 20 cmH$_2$O). Bars as in Fig. 1. ○ or + symbols, outliers. $* P < 0.05$ and $** P < 0.01$ vs. normal group. $\phi P < 0.05$ vs. SDB-1 group.

Table 2. *Results of exponential curve fitting*

	Normal Subjects (ODI $\leqq 5$)	SDB-1 ($5 < ODI < 20$)	SDB-2 (ODI $\geqq 20$)
Velopharynx			
B	1.47 ± 0.61	1.40 ± 0.55	1.76 ± 0.93
K	0.12 ± 0.05	0.19 ± 0.09†	0.18 ± 0.05*
P_C', cmH$_2$O	-3.77 ± 3.44	0.90 ± 1.34†	2.78 ± 2.78†‡
P_{50}, cmH$_2$O	6.58 ± 2.50	4.16 ± 1.44†	4.25 ± 1.25†
R^2	0.93 ± 0.04	0.95 ± 0.03	0.95 ± 0.03
Oropharynx			
B	1.85 ± 1.25	2.89 ± 1.32	7.31 ± 21.8
K	0.13 ± 0.04	0.18 ± 0.09*	0.20 ± 0.09*
P_C', cmH$_2$O	-5.47 ± 4.90	-1.92 ± 6.36*	0.48 ± 3.62†
P_{50}, cmH$_2$O	6.10 ± 2.24	6.64 ± 10.8	3.94 ± 1.52
R^2	0.93 ± 0.05	0.95 ± 0.03	0.94 ± 0.05

Values are means $\pm$ SD. Estimated closing pressure (P_C') and half-dilation pressure (P_{50}) were calculated by $P_C' = \ln (B/A_{max})/K$ and $P_{50} = \ln (2)K^{-1}$ where B and K are constants obtained by fitting pressure-area relationship of each pharyngeal segment to exponential function $A = A_{max} - B * \exp (- K * P_{aw})$ where A, A_{max}, and P_{aw} denote cross-sectional area of pharynx, maximum area of pharynx, and airway pressure, respectively. Quality of fit is provided by coefficient R^2. K characterizes shape of exponential curve. * $P < 0.05$, † $P < 0.01$ vs. normal group; ‡ $P < 0.05$ vs. *SDB-1 group.*

was not as clear as for the VP. Patients in SDB-1 group had A_{maxOP} equivalent to normal subjects but had higher P_{COP}' than normal subjects. Most of the patients in SDB-2 group had smaller A_{maxOP} and higher P_{COP}' than normal subjects. Half of the subjects in the SDB-1 and SDB-2 groups (21 of 40) had subatmospheric P_{COP}'.

Curve-fitting analysis estimated P_C for each pharyngeal segment (Table 2). Mean values of P_{CVP}' of SDB-1 and SDB-2 groups (0.90 ± 1.34 and 2.78 ± 2.78 cmH$_2$O, respectively) were significantly higher than that of normal subjects (-3.77 ± 3.44 cmH$_2$O). The overlap in

P_{CVP}' between normal subjects and the two apneic groups was minimal. Mean P_{COP}' of SDB-1 and SDB-2 groups (-1.92 ± 6.36 and 0.48 ± 3.62 cmH$_2$O, respectively) was significantly higher than that of normal subjects (-5.47 ± 4.90 cmH$_2$O), although the data overlapped considerably.

P_{50} values for the VP in SDB-1 and SDB-2 (4.16 ± 1.44 and 4.25 ± 1.25 cmH$_2$O, respectively) were significantly smaller than that for normal subjects (6.58 ± 2.50 cmH$_2$O). P_{50} at the OP did not differ among the groups (Table 2).

Correlation of Mechanical Parameters With Nocturnal Desaturation

The results of the multivariate regression analysis reduced the factors stepwise to three terms (A_{maxVP}, B_{VP}, and P_{CVP}') that significantly correlated with log (ODI). That all the significant factors were mechanical parameters of the VP suggests that mechanical properties of the VP determine breathing pattern during sleep. Results of multivariate analysis for these three are demonstrated in Table 3. Among the three parameters, P_{CVP}' was the only variable with a high t-value, indicating that P_{CVP}' was the best correlate of nocturnal desaturation.

Correlation of Mechanical Parameters Between the VP and the OP

Figure 4 demonstrates the relationship between P_{CVP}' and P_{COP}' for all the subjects. The data points of 48 of 57 subjects were located below the identity line, while those of 9 subjects were located above the identity line. P_{COP}' correlated significantly with P_{CVP}' ($R = 0.590$, $P < 0.00001$).
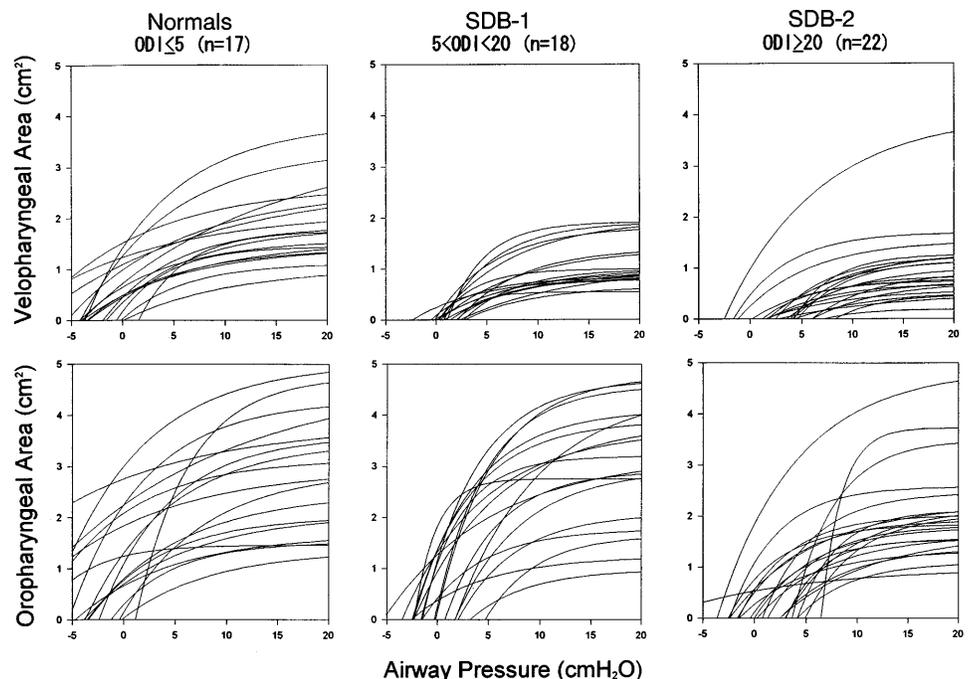

Fig. 3. Each curve represents static pressure-area relationship of passive pharynx of 1 subject. ODI, oxygen desaturation index (no. of oxygen desaturations exceeding 4% from baseline); *n*, no. of subjects. By using nonlinear least squares technique, curve was obtained by fitting measured pressure-area data to an exponential function, $A = A_{max} - B * \exp(-K * P_{aw})$, where A denotes cross-sectional area of pharynx and B and K are constants. Note that VP curves of patients with SDB lie below and to right of curves for normal subjects.

Table 3. *Results of multivariate linear regression analysis of relationship of log (ODI) and A_{maxVP}, B_{VP}, PC'_{VP}*

Variables	Estimate $\pm$ SE	t-Value
A_{maxVP}	-0.1251 ± 0.1158	-1.0807
B_{VP}	0.0862 ± 0.1014	0.8498
PC'_{VP}	0.0754 ± 0.0246	$3.0626*$

Values are means $\pm$ SE. A_{maxVP}, maximum area of velopharynx; B_{VP}, constant obtained by exponential-fitting analysis; PC'_{VP}, velopharyngeal closing pressure. $*P < 0.005$.

DISCUSSION

We obtained static pressure-area relationships of the passive pharynx in anesthetized, completely paralyzed adult humans and observed that the relationship for patients with SDB differed from that for age and BMI-matched normal controls. The pressure-area curve of the VP for patients with SDB was below that for normal controls, having a smaller A_{max} and higher PC. In addition, the pharynx of apneic subjects was more vulnerable to pressure change near PC independent of the size of the pharynx, because the K values for the VP and the OP in patients with SDB were greater than in normal subjects. The results support the anatomic hypothesis that sleep apneic subjects have a structurally narrowed and collapsible pharynx. We also observed that PC_{VP} correlated with the frequency of nocturnal desaturations and PC_{OP}.

Design of the Study

Selection and classification of the subjects. Mean BMI of apneic groups in this study appears to be smaller than that of other groups reported in the literature (8, 25). On the other hand, BMI of the normal controls selected to match body size appears to be larger than that of typical normal subjects. Accordingly, each group of samples may not reflect a whole population of each category. Because our aim was to compare static mechanics between patients with OSA and age- and BMI-matched normal controls, we believe that the

hypothesis was satisfactorily tested in our sample despite this potential limitation.

Because we did not perform polysomnography, classification of the subjects may be questionable to some extent. However, we tried to minimize the error in the classification by selecting the normal subjects from the population with, presumably, low prevalence of OSA and by selecting the patients with SDB from symptomatic patients who visited our sleep clinic in addition to use of the oximetry criteria. Subjects were classified on the basis of nocturnal oximetry data. ODI is known to be a highly specific but insensitive parameter in diagnosis of OSA (7). Therefore, whereas all subjects assigned to SDB groups are likely to have OSA, some subjects in the normal group may have SDB. The additional use of CT_{90}, however, is reported to increase the sensitivity in diagnosis of OSA (9). All the subjects in normal group had $CT_{90} = 0$. Accordingly, we believe that our grouping of the subjects is reasonably accurate, with the caveat that some normal subjects may have had OSA. Such misclassification would have only obscured group differences in mechanical parameters of the passive pharynx.

Evaluation of static mechanics of the passive pharynx. The size of the pharyngeal lumen is determined by balance between outward forces developed by active contraction of UA muscles and inward forces resulting from subatmospheric luminal pressure during inspiration (4, 27). Use of a schematic model of a balance (Fig. 5) explains well the balance concept. The model has UA muscle activities and Paw on either side of a fulcrum that is considered to represent intrinsic mechanical properties of the passive pharynx, that is, anatomy of the pharynx. In this model, pharyngeal patency is determined by complicated interaction among the three factors, i.e., UA muscle activities, Paw, and anatomy of the pharynx. The aim of the present study is to ask whether the position of the fulcrum differs between normal subjects and sleep apneic subjects. Accordingly, we evaluated the mechanics of the pharynx while controlling the other two factors.

During wakefulness, the UA muscles are actively contracting while fluctuation of Paw is minimal. Although sleep may profoundly reduce the UA muscle activity, this activity and Paw generated vary temporally in relation to stimuli such as chemostimulation and arousal (6). Accordingly, mechanistic interpretation of data regarding the size and mechanics of the pharynx during wakefulness and sleep is uncertain. For instance, Gleadhill et al. (8) found that differences in UA collapsibility, defined by critical pressure, distinguish snorers from patients with periodic hypopneas and apneas. However, they attributed the results to disturbances of neuromuscular control in OSA patients, even though pharyngeal muscle activities were not compared. Other researchers (30) comparing patients with OSA and normal subjects have reported differences in airway size during wakefulness. These differences are attributed to structual differences, even though the relative activity of UA muscles in the two groups is unknown.
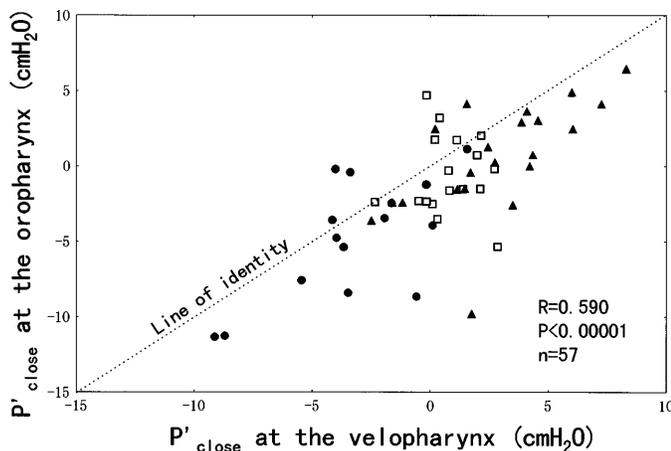

Fig. 4. Relationship between VP PC (PC_{VP}') and OP PC (PC_{OP}') for all the subjects. ●, Normal group; □, SDB-1 group, and ▲, SDB-2 group.
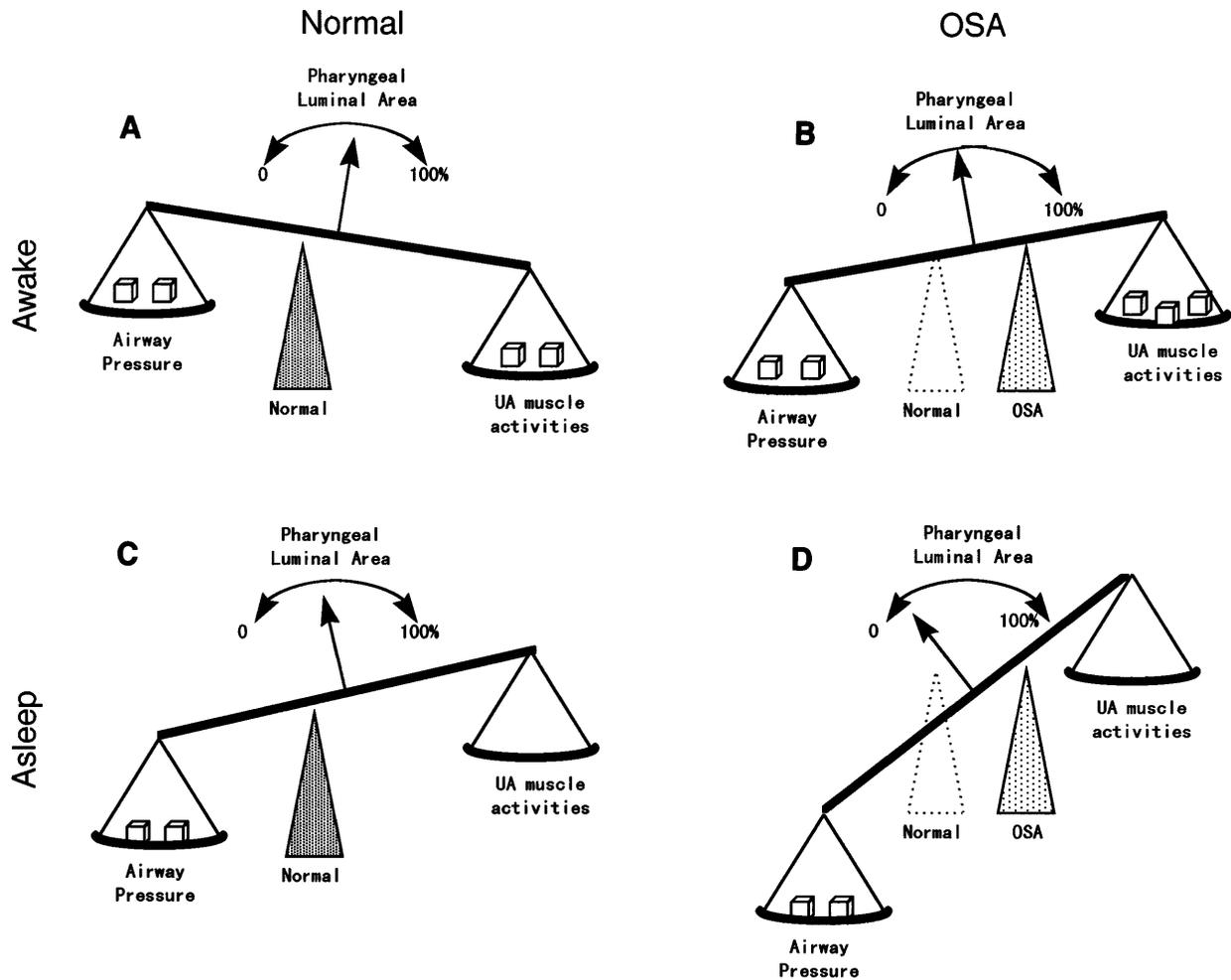
Fig. 5. Schematic model explaining pharyngeal airway patency, showing upper airway (UA) muscle activities and Paw on either side of fulcrum that represents intrinsic mechanical properties of pharynx, i.e., anatomy of pharynx. OSA, obstructive sleep apnea. Fulcrum of sleep apneic subjects (*B* and *D*) is suggested to be to right side of normal subjects (*A* and *C*).

Other than using muscular paralysis, only the single-breath test (SBT) method, in which Paw is abruptly reduced from a high holding pressure to a preselected lower test pressure at the end of inspiration, allows evaluation of the anatomy of the pharynx by greatly reducing neuromuscular factors (15, 21, 25). During natural or diazepam-induced sleep, the SBT method determines the sites of narrowing and Pc of the hypotonic pharynx in patients with OSA (25). Furthermore, the site of pharyngeal narrowing determined by the SBT method successfully predicted outcome of surgery for OSA (21).

In the present study, neuromuscular factors were completely eliminated by use of muscular blockade under general anesthesia. Therefore, in our experimental design, the weight of the right side of the scale in Fig. 5 was reduced to zero. By manipulating Paw, i.e., the weight on the left scale, and by observing pharyngeal luminal area (top gauge), the position of the fulcrum can be compared between normal and apneic subjects. Although our method successfully separated anatomic factors from the neuromuscular factors, one should bear in mind that there are minimal activities of

pharyngeal dilator muscles at the initiation of apnea in normal sleep. Therefore, Pc presented here may not ultimately reflect the collapsibility of the pharynx during natural sleep.

Furthermore, static pressure-area relationship of the pharynx reported here may not be identical to the "tube law" of the pharynx, i.e., transmural pressure-area relationship of the pharynx. Because the transmural pressure is defined as the difference between luminal and tissue pressure, the luminal pressure-area relationship reported here would reflect the characteristics of the tube law so long as the tissue pressure were to be constant. However, Schwartz et al. (32) suggested that tissue pressure changes when luminal pressure changes. Another consideration is that lung volume systematically varied with Paw. Lung volume is known to influence mechanical properties of the pharynx (11, 34). Therefore, the static pressure-area relationship would be different if lung volume were to be maintained constant. Although further study designed to control lung volume is necessary, we believe that the influence of lung volume does not change our conclusions, be-

cause changes of lung volume with Paw are likely to be equivalent in BMI-matched normal and apneic groups.

Passive Mechanics of the Pharynx in Patients With OSA and Normal Subjects

Comparison of the static pressure-area relationships between the groups indicates that cross-sectional area of the pharynx of OSA patients was significantly smaller than that of normal subjects, for a constant Paw. Therefore, the fulcrum of OSA patients is inferred to be shifted to the right of normal in the balance model of Fig. 5. Accordingly, for any given luminal pressure, sleep apneic subjects have a lower cross-sectional area of the pharynx than normal subjects. This structural abnormality can be attributed to abnormalities of bony structures and/or soft tissue surrounding the pharyngeal airway.

With regard to abnormal bony structures, several cephalometric studies reported that patients with OSA have craniofacial abnormalities, such as retrognathia and micrognathia, that correlate with the severity of OSA (17, 23). Furthermore, magnetic resonance imaging (MRI) study demonstrated that apnea-hypopnea index was related to the size of the region enclosed by the mandible as well as the weight (35). Although these investigations strongly suggest the importance of bony structures in the pathogenesis of OSA, a more recent analysis, using similar MRI techniques, found no significant difference in bony structures between normal subjects and sleep-apneic subjects (30). Although we did not evaluate UA bony structures in our subjects, none of them had clinically apparent facial abnormalities.

Abnormalities of soft tissue surrounding the pharyngeal airway can contribute to OSA, because an increase in mass inside the enclosure provided by bony structure at the level of the pharynx may limit the size of the pharyngeal lumen. The smaller A_{max} and higher Pc in sleep apneic subjects observed here support this speculation. Increases in tongue or soft palate volume (22, 29), volume of parapharyngeal fat (13, 36), or thickness of the lateral pharyngeal muscular walls (30) may contribute to a decrease in the size of the pharyngeal airway. Decrease in longitudinal tension along the pharynx can also increase the collapsibility of the pharynx (40, 41).

Correlational Analyses

Multivariate regression analysis indicated that Pc_{VP} was the best correlate of the frequency of nocturnal desaturations. This might suggest that Pc, independent of A_{max}, may play a significant role in the pathogenesis of OSA, although both parameters significantly differed between normal subjects and sleep apneic subjects. Schwartz et al. (31–33) and Smith et al. (38) succeeded in applying the Starling resistor model to account for airflow limitation by the pharynx. Furthermore, we also previously reported that the passive pharynx behaves like the Starling resistor model (15). In a collapsible tube, such as the Starling resistor

model, the size as well as the collapsibility of the tube is a significant factor determining maximum airflow through the collapsible tube (12, 18, 19, 43). Only when the upstream pressure in the collapsible tube exceeds a critical pressure, which is considered to be identical to the Pc, does the air flow through it (26). The resistance of the tube is infinite below the Pc, while the tube acts as a variable resistor for the air above the Pc. In other words, the size and the collapsibility of the tube play an important role in determining maximum airflow only when luminal pressure exceeds Pc. This may account for the paradox that the elderly men have larger cross-sectional area, although the prevalence of SDB events is increased in these subjects (5). Pc in elderly men may explain the paradox. Similarly, a marked male predominance of OSA may be possibly due to higher Pc in men than in women, because Brooks and Strohl (3) demonstrated that during wakefulness men have larger but more collapsible pharynxes than women.

Correlation between Pc_{VP} and Pc_{OP} may suggest mechanical interdependence between these segments. Because the tongue is positioned just ventral to the soft palate, the tongue could push the soft palate dorsally, changing mechanical properties of the VP. This may be supported by our previous finding that forward displacement of the tongue produced by mandibular advancement shifted the static pressure-area relationship of the VP (16). Similarly, Schwartz et al. (33) found that tongue protrusion achieved by electrical stimulation of the hypoglossal nerve reduced the collapsibility of the flow-limiting site, which is considered to be the VP. Although our results strongly suggest importance of the VP in OSA, derangements of pharyngeal mechanics at this level may reflect altered OP mechanics.

In summary, by comparing static pressure-area relationship of the passive pharynx between patients having SDB with age- and BMI-matched normal subjects, we tested the anatomic hypothesis that persons with sleep apnea have a more narrow and collapsible pharynx than normal persons. Our findings validate the hypothesis in a selected group of patients and normal subjects. Mechanical characteristics of the VP, especially its Pc, may be of particular importance in determining the frequency of nocturnal desaturations. Thus characteristics of the VP may depend to some extent on mechanics of the OP.

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