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Research Article

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Paradoxical Glottic Narrowing in Patients with Severe Obstructive Sleep Apnea

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Abstract

Most patients with obstructive sleep apnea have increased pharyngeal collapsibility (defined in the present study as an increased lung volume dependence of pharyngeal area), which predisposes them to upper airway occlusion during sleep. However, there are patients with severe obstructive sleep apnea who have low-normal pharyngeal collapsibility. The factors leading to nocturnal upper airway obstruction in such patients have not been ascertained. We studied 10 overweight male patients with severe obstructive sleep apnea and low-normal pharyngeal collapsibility to determine the site of upper airway pathology in these patients. We found that all 10 patients exhibited paradoxical inspiratory narrowing of the glottis during quiet tidal breathing. This phenomenon was not observed in a matched group of 10 snoring, nonapneic male controls. We conclude that paradoxical glottic narrowing may be a contributing factor in the pathogenesis of upper airway obstruction in patients with severe obstructive sleep apnea who have low-normal pharyngeal collapsibility.

Introduction

Idiopathic obstructive sleep apnea (OSA)[1] is characterized by repeated episodes of nocturnal upper airway obstruction. Although the pathogenesis of this disorder is still unknown, it has been shown that these patients have abnormal pharyngeal structure, as reflected by a reduction in pharyngeal cross-sectional area (1–3). In addition, they also have abnormal pharyngeal function that is manifested by increased pharyngeal collapsibility (4, 5), whether assessed by measuring pharyngeal compliance from the pressure-area curves or by measuring the lung volume dependence of pharyngeal area (PLVD), as was done in the present study. These abnormalities, when superimposed on the normal reduction in pharyngeal muscular tone which occurs during sleep, may lead to pharyngeal obstruction (6).

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1. *Abbreviations used in this paper:* A, area; ERV, expiratory reserve volume; FR, flow ratio; FRC, functional residual capacity; OSA, obstructive sleep apnea; PLVD, lung volume dependence of pharyngeal area; RV, residual volume.

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We recently encountered obese patients with severe idiopathic OSA who had low-normal pharyngeal collapsibility. This finding led us to postulate that in these patients the major site of upper airway pathology might not be located in the pharynx but in the glottis, which is normally the narrowest part of the upper airway.

Methods

We studied 10 snoring, overweight (body mass index 39±8 kg/m^2), middle aged (43±12 yr), male patients with severe sleep apnea (apnea/hypopnea index 72±19/hr), who had low-normal pharyngeal collapsibility. They were selected from a group of 57 patients with OSA on the basis of a PLVD (see below) that was less than the mean value of 0.82 cm^2/liter established in our laboratory for nonapneic, overweight, male snorers. This reference value of PLVD was obtained from a previous study (unpublished PLVD observations) of 31 nonapneic, overweight, male snorers taken from the same clinic (Sleep, Nose, and Sinus clinic at St. Michael's Hospital) as the subjects in this study.

We also studied a control group consisting of 10 male, nonapneic (apnea/hypopnea index 4±3/h) snorers matched for age (41±10 yr) and body mass index (35±9 kg/m^2). To compare the characteristics of our study group with those of the more common patients with OSA, we selected a group of 10 patients having high pharyngeal collapsibility and matched them as closely as possible to the study group with respect to the severity of OSA (apnea/hypopnea index 78±25), age (53±10), and body mass index (39±6).

In all 30 subjects, we obtained upper airway area measurements (7) and sleep studies (8) which were analyzed by experienced technicians who were unaware of the purpose of the study. An episode of obstructive apnea was identified as an absence of tidal volume excursions for at least 10 s, during which there were unequivocal, paradoxical movements of the chest wall and the abdomen. An episode of obstructive hypopnea was defined as a reduction in tidal volume of at least 50% from the baseline, lasting at least 10 s, and accompanied by a reduction in oxygen saturation of at least 4%. We also measured maximum expiratory flow-volume curves using a wedge spirometer, as well as functional residual capacity (FRC) by body plethysmography. Residual volume (RV) was calculated by subtracting expiratory reserve volume from FRC.

Using the acoustic reflection technique, which has been described in detail previously (4, 7, 9, 10), we obtained a total of 128 measurements of upper airway area at FRC and 32 measurements at RV in each awake, seated subject. The average pharyngeal areas were calculated in a manner similar to that used in our previous study (7), except that the "pharynx" was now defined as the region extending from the start of the mouthpiece to the glottic minimum. To assess pharyngeal collapsibility, we calculated the lung volume dependence of pharyngeal cross-sectional area (PLVD), defined as the difference in pharyngeal area between FRC (A_{FRC}) and RV (A_{RV}) normalized to the expiratory reserve volume (ERV), i.e., $(A_{FRC} - A_{RV})/ERV$.

Glottic cross-sectional areas were measured during quiet, tidal breathing. A total of 128 measurements were obtained in each subject and measurements obtained at midexpiration and midinspiration of each tidal breath were used for analysis. The "glottic area" was defined as the area corresponding to the glottic minimum on the area-distance plot.

One-way analysis of variance was used to compare all data among the three groups. The level of statistical significance was taken as $P < 0.01$.

Results

All three groups were similar in terms of body mass index and weight (Table I), but the OSA subjects tended to be somewhat older and shorter, although the difference was not statistically significant. Lowest nocturnal oxygen saturation was significantly lower in patients with OSA than in nonapneic controls (Table I). FRC and RV were slightly higher and ERV lower in the OSA patients with high PLVD than in the other two groups. In the case of FRC, the difference was statistically significant, but in the case of RV and ERV the difference did not reach statistical significance. Vital capacity, forced expired volume in 1 s, and the midvital capacity flow ratio (FR) (FR is the ratio of maximal expiratory to inspiratory flow rates) were similar among all three groups (Table II). Pharyngeal cross-sectional areas at FRC were similar among the three groups, but the areas at RV were somewhat higher in the study group (Table III), although the difference was not statistically significant according to the selected significance criterion of $P < 0.01$. As expected from our selection criteria, the study patients with OSA had lower PLVD than both of the other groups (-0.06 ± 0.44 cm^2/liter vs. 0.55 ± 0.35 cm^2/liter for the nonapneic snorers and 2.93 ± 2.02 cm^2/liter for the OSA subjects).

There was no significant difference in the midinspiratory glottic areas among the three groups, and the same was true for the midexpiratory glottic areas (Table III). However, in both "control" groups, midinspiratory glottic area was either the same (two nonapneic and four apneic controls) or greater (eight nonapneic and six apneic controls) than the midexpiratory area, while in all 10 patients with severe OSA and low PLVD, the converse was true; they all had paradoxical midinspiratory narrowing of the glottis (Table III).

The percent change in glottic area between midinspiration and midexpiration, normalized to midinspiratory area in all 30 subjects, is shown in Fig. 1. Nonapneic controls showed an increase in glottic area from expiration to inspiration ($7 \pm 8\%$), apneic controls demonstrated a $12 \pm 17\%$ increase, while patients with OSA and low PLVD showed a decrease in glottic area of $32 \pm 24\%$ ($P < 0.00001$). No significant correlation was found between glottic area and its change from inspiration to expiration and the apnea/hypopnea index or the lowest nocturnal oxygen saturation.

Discussion

In the present study we describe patients with severe OSA in whom upper airway obstruction cannot be accounted for by increased pharyngeal collapsibility. We found that these patients have paradoxical midinspiratory narrowing of the glottis, which may predispose them to upper airway obstruction during sleep. These conclusions are based on measurements obtained by using the acoustic reflections technique. This method has been validated by a number of groups which used various methods, including direct measurements in airway casts (11), radiographic views of the airway (12), and computed tomography scans (9, 10).

To date, most of the attention regarding the pathogenesis of OSA has focused on pharyngeal structure and function. A number of investigators using computed tomography scans, x-ray cephalometry, and acoustic reflections have confirmed the presence of pharyngeal narrowing in patients with OSA (1–3). Various other indices of pharyngeal function, such as closing pressure (5), dynamic upper airway resistance (13, 14),

*Table I. Anthropometric and Sleep Data in all Subjects**

	Age	Weight	Height	BMI	AHI	LO_2
	yr	*kg*	*cm*	*kg/m^2*	*No./hr*	*%*
	OSA study patients (low PLVD)					
1.	47	148	175	48	102	65
2.	62	130	183	39	49	49
3.	45	110	176	36	92	17
4.	47	102	171	35	50	30
5.	28	180	183	54	46	64
6.	34	108	180	33	74	88
7.	28	144	178	45	80	70
8.	52	90	172	30	68	79
9.	33	102	187	29	70	83
10.	53	146	182	44	85	14
Mean	43	126	179	39	72	56
SD	12	28	5	8	19	27
	Non-OSA controls					
1.	40	73	163	27	0	97
2.	30	172	178	54	6	90
3.	39	157	185	46	9	87
4.	26	127	181	39	4	86
5.	45	84	167	30	5	89
6.	33	106	183	32	4	87
7.	56	107	175	35	5	92
8.	55	88	170	30	0	89
9.	42	98	169	34	2	88
10.	45	84	184	25	9	85
Mean	41	110	176	35	4	89
SD	10	33	8	9	3	3
	OSA patients (high PLVD)					
1.	45	105	173	35	87	15
2.	63	77	156	32	78	48
3.	65	102	169	36	128	56
4.	54	142	174	47	60	39
5.	59	140	180	43	57	20
6.	35	121	170	42	89	60
7.	62	143	172	48	42	55
8.	56	106	175	35	60	60
9.	53	116	156	42	96	73
10.	42	88	171	30	79	75
Mean	53	114	171	39	78	49
SD	10	23	6	6	25	23
P‡	0.03	0.42	0.03	0.45	—	0.0004

* BMI, body mass index; AHI, apnea/hypopnea index; LO_2, lowest nocturnal oxygen saturation; PLVD, lung volume dependence of pharyngeal area.

‡ P value as obtained from the analysis of variance comparing all three groups.

*Table II. Pulmonary Function Data**

	FRC	RV	ERV	FEV_1	FVC	FR
	% pred		liter	% pred		
	OSA study patients (low PLVD)					
1.	78	79	1.0	92	85	0.7
2.	110	148	0.6	103	121	1.0
3.	78	90	0.9	129	118	1.0
4.	67	87	0.5	110	110	0.9
5.	49	48	1.2	100	86	0.6
6.	88	86	1.9	125	133	0.6
7.	82	58	2.0	128	128	1.0
8.	104	143	0.4	114	109	0.5
9.	95	103	2.1	92	103	0.5
10.	58	75	0.5	91	89	0.6
Mean	81	92	1.1	108	108	0.7
SD	19	32	0.7	15	17	0.2
	Non-OSA controls					
1.	63	88	0.8	113	103	0.9
2.	93	137	0.9	104	103	0.6
3.	58	94	0.4	117	118	0.6
4.	79	127	0.8	66	71	0.6
5.	76	86	0.9	106	92	0.9
6.	91	110	1.5	117	113	0.7
7.	73	102	0.3	118	102	0.7
8.	79	88	0.7	108	107	0.9
9.	117	168	0.4	85	83	0.8
10.	90	105	1.5	111	109	0.5
Mean	84	111	0.8	105	100	0.7
SD	16	26	0.4	17	14	0.2
	OSA patients (high PLVD)					
1.	121	185	0.4	65	81	0.3
2.	114	97	0.1	124	126	0.3
3.	128	137	0.8	140	118	0.9
4.	127	180	0.4	104	103	0.9
5.	68	96	0.4	77	64	1.0
6.	127	211	0.4	53	84	0.3
7.	145	196	0.3	50	81	0.4
8.	75	79	0.6	111	97	1.0
9.	105	143	0.5	92	107	0.3
10.	74	90	0.7	118	107	0.7
Mean	108	141	0.5	93	97	0.6
SD	27	49	0.2	31	19	0.3
P‡	0.01	0.02	0.02	0.31	0.32	0.39

* FRC, functional residual capacity; RV, residual volume; ERV, expiratory reserve volume; FEV_1, forced expired volume in 1 s; FVC, forced vital capacity; FR, ratio of expiratory to inspiratory flow rates at 50% of the vital capacity; % pred, percent of predicted value; PLVD, lung volume dependence of pharyngeal area.
‡ P value as obtained from the analysis of variance comparing all three groups.

*Table III. Pharyngeal and Glottic Data**

	Aph_{FRC}	Aph_{RV}	PLVD	Agl_{INS}	Agl_{EXP}
	cm^2		cm^2/liter	cm^2	
	OSA study patients (low PLVD)				
1.	3.20	3.90	−0.70	0.95	1.55
2.	3.00	2.80	0.33	0.95	1.55
3.	3.10	2.75	0.39	1.70	1.90
4.	3.00	2.90	0.20	1.05	1.35
5.	3.60	3.30	0.25	1.55	2.30
6.	3.60	3.40	0.11	1.15	1.35
7.	3.30	3.30	0	1.80	2.05
8.	2.30	2.55	−0.63	1.85	2.00
9.	3.15	2.90	0.12	1.00	1.60
10.	3.85	4.20	−0.70	1.55	1.70
Mean	3.21	3.20	−0.06	1.36	1.74
SD	0.43	0.53	0.44	0.37	0.32
	Non-OSA controls				
1.	4.85	4.55	0.38	1.85	1.75
2.	2.90	2.45	0.50	1.95	1.85
3.	3.45	3.10	0.88	0.95	0.90
4.	3.70	3.45	0.31	2.60	2.55
5.	3.10	2.10	1.11	1.25	1.00
6.	3.80	2.90	0.60	2.45	1.90
7.	2.60	2.30	1.00	1.40	1.40
8.	2.35	2.35	0	0.90	0.80
9.	2.55	2.45	0.25	1.25	1.25
10.	3.55	2.90	0.43	1.60	1.55
Mean	3.29	2.86	0.55	1.62	1.50
SD	0.75	0.73	0.35	0.59	0.54
	OSA patients (high PLVD)				
1.	4.15	3.60	1.38	1.70	1.70
2.	4.10	3.35	7.50	2.50	2.10
3.	2.75	1.65	1.44	1.80	1.65
4.	3.35	1.25	5.25	1.25	1.25
5.	4.45	3.15	3.25	2.20	2.20
6.	2.85	1.95	2.25	1.65	1.55
7.	3.70	2.70	3.33	2.05	0.95
8.	3.45	2.60	1.42	1.05	1.05
9.	2.80	2.00	1.60	1.30	1.25
10.	2.90	1.60	1.86	0.95	0.70
Mean	3.45	2.39	2.93	1.65	1.44
SD	0.63	0.81	2.02	0.51	0.49
P‡	0.68	0.05	—	0.37	0.33

* Aph_{FRC}, pharyngeal area at FRC; Aph_{RV}, pharyngeal area at RV; PLVD, lung volume dependence of pharyngeal area; Agl_{INS}, glottic area at midinspiration; Agl_{EXP}, glottic area at midexpiration.
‡ P value as obtained from the analysis of variance comparing all three groups.

and pharyngeal compliance (4) are abnormal in patients with OSA. Thus, the current hypothesis regarding the pathophysiology of most cases of OSA is that these patients have relatively small and "compliant" upper airways when compared with nonapneic controls. These structural and functional abnormalities of the pharynx, when superimposed on the normal hypotonia of pharyngeal muscles that is present during sleep, are thought to facilitate complete pharyngeal occlusion (6).

In our ongoing investigations of patients with OSA, we found that there was a subgroup of patients with severe disease

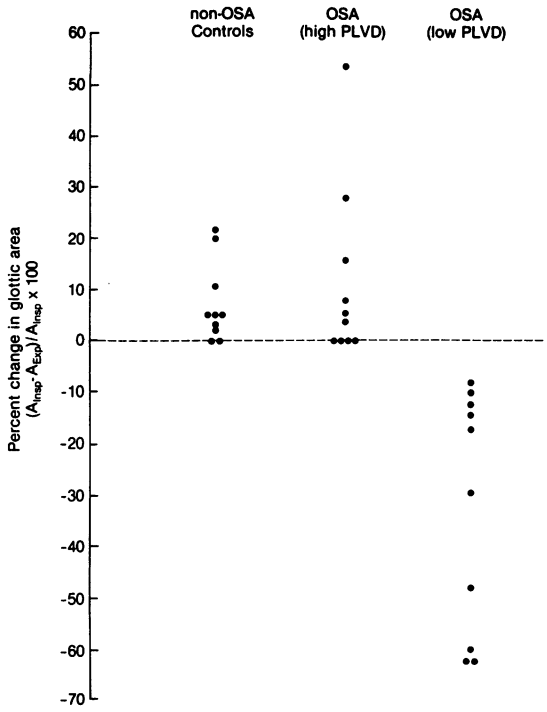

Figure 1. Percent change in glottic area during quiet tidal breathing in all three groups. A_{Insp}, area of glottis at midinspiration; A_{Exp}, area of glottis at midexpiration, PLVD, lung volume dependence of pharyngeal area.

who did not fit into this schema because they had low-normal pharyngeal collapsibility. Although this finding was relatively uncommon, we could not explain the pathogenesis of their OSA on the basis of abnormalities in pharyngeal properties. These results prompted us to investigate other mechanisms that could account for the obstructive apneas. Previous reports have identified the glottis as a possible site of airway obstruction. For example, Rivlin et al. (3) noted that the glottic areas, as well as the pharyngeal areas, were reduced in patients with OSA. In addition, Wilms et al. (15) visualized the upper airway of patients with OSA and found that 8% had the larynx as the primary site of obstruction. Since the glottis is the narrowest segment of the upper airway and since glottic abnormalities are relatively common in patients with OSA (1, 3, 15), we focused on this region in our investigation of the mechanisms of obstruction.

Glottic movements during quiet, tidal breathing have been studied extensively in normal subjects, and it is well established that glottic area increases during inspiration and decreases during expiration (16). The increase in glottic aperture during inspiration is thought to be due to activation of laryngeal abductors that overcome the subatmospheric laryngeal pressure that tends to adduct the larynx (17). It is conceivable that the paradoxical, inspiratory glottic-narrowing observed in our patients reflects an unexplained reduction in laryngeal abductor muscle tone leading to passive narrowing of the glottis during inspiration. This could also explain the obstruction during sleep, since further glottic narrowing might be anticipated simply as a result of generalized sleep-induced relaxation of upper airway muscles, including those of the larynx (6, 18). Another possibility is that these patients have abnormal regulation of laryngeal muscles, leading to active, inward, paradoxical movement of the glottis during inspiration. The precise contribution of each of these mechanisms in the development of the obstruction may be difficult to ascertain, since the neuronal control of laryngeal musculature is complex and is mediated by a variety of reflexes arising from pulmonary and laryngeal receptors (16, 17).

Although the number of patients studied is too small to estimate the incidence of reduced pharyngeal collapsibility among patients with OSA, our results indicate that the majority of patients have increased pharyngeal collapsibility. We compared the characteristics of our study group with those of the more usual group of patients with OSA who had increased pharyngeal collapsibility. We found no significant difference in absolute glottic areas, maximum inspiratory flows, or mid-vital capacity flow ratios. Pharyngeal areas at RV and the ERVs were higher in the OSA patients with glottic paradox, but this reflects the selection criteria (based on low PLVD) used to identify these patients. We did find somewhat lower lung volumes in the study group compared with the OSA group, but this cannot explain the obstruction since the study group values were similar to those observed in the non-OSA controls.

We should point out, however, that glottic paradox is not unique to OSA patients with decreased pharyngeal collapsibility. Although not presented in the current report, we have observed patients with OSA who have both glottic paradox and high pharyngeal collapsibility. These findings imply that some patients with OSA are predisposed to upper airway occlusion from abnormalities in more than one segment of the upper airway. Similarly, paradoxical movements of the glottis have been described in patients without any apparent sleep-related breathing disorders, e.g., in some patients with asthma (19).

Our results were obtained while our subjects were awake and seated. The effect of posture and sleep state may have important influences on upper airway morphology. The available evidence indicates, however, that these factors would tend to aggravate, rather than ameliorate, any preexisting abnormalities of the upper airways. For example, assumption of the supine posture reduces pharyngeal area in normal individuals (20) as well as in patients with OSA (21). Issa and Sullivan (5, 22) showed a progressive reduction in the negative pressure necessary to collapse the pharynx during sleep in nonapneic nonsnorers, nonapneic snorers, and patients with OSA. To the extent that these sleep-induced changes affect the glottis, the abnormalities found in the present study may be worse during sleep.

Our findings may have important clinical implications regarding the therapy of OSA. Uvulopalatopharyngoplasty has been proposed as a treatment for this disorder, but it is successful only in about half of the patients (23). If the glottis is the major site of obstruction in some patients with OSA, then uvulopalatopharyngoplasty, which affects only the retropalatal region, would be unlikely to benefit these patients. Collett et al. (24) have shown that application of continuous positive airway pressure may temporarily reverse glottic narrowing in patients with acute asthma. This mechanism may explain the efficacy of continuous positive airway pressure in some patients with OSA who are treated with this modality (25).

In summary, we have described a group of patients with severe OSA who do not have increased pharyngeal collapsibil-

ity, but exhibit paradoxical narrowing of the glottis during inspiration. These findings indicate that upper airway pathology in patients with OSA may occur at different sites along the upper airway.

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