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Original Article

Analysis of the aerodynamic characteristics of the upper airway in obstructive sleep apnea patients

Xing-Long Wen [a,1], Bin-Zhang Wu [b,1], Yang Li [a], Biao Yi [a*], Xin Peng [a]**

[a] *Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology & National Center for Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, Beijing, PR China*

[b] *First Clinical Division, Peking University School and Hospital of Stomatology & National Center for Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, Beijing, PR China*

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Airway resistance

Abstract *Background/purpose:* This study was designed to explore upper airway aerodynamic characteristics in individuals diagnosed with obstructive sleep apnea (OSA) and to evaluate correlations between these characteristics and other anatomical upper airway findings in these patients.
Materials and methods: This was a retrospective study of 40 OSA patients (22 male, 18 female) who were stratified into groups with mild, moderate, and severe disease based upon overnight polysomnographic (PSG) recording results. Newtom5G cone-beam CT scans (CBCT) were conducted for all patients, and the resultant images were used to reconstruct three-dimensional images of the upper airways which were used to calculate aerodynamic characteristics. Differences in these characteristics between groups were evaluated with one-way ANOVAs, while relationships between anatomical and aerodynamic characteristics were assessed through Pearson correlation analyses.
Results: The aerodynamic of the upper airway has typical characteristic in severe group. There was a significant negative correlation in severe group between resistance during inspiration (Rin) and volume (V) ($r = -0.693$, $P = 0.013$), minimum axial area (MMA) ($r = -0.685$, $P = 0.014$), and lateral dimension (LAT) ($r = -0.724$, $P = 0.008$), resistance during expiration (Rex) and LAT ($r = -0.923$, $P < 0.001$).

* Corresponding author. Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, No.22, Zhongguancun South Avenue, Haidian District, Beijing, 100081, PR China.
** Corresponding author. Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, No.22, Zhongguancun South Avenue, Haidian District, Beijing, 100081, PR China.
E-mail addresses: yibiaopku@163.com (B. Yi), pxpengxin@263.net (X. Peng).
[1] These authors contributed equally to this work.

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Conclusion: This study showed that airway resistance during inspiration and expiration are most closely associated with upper airway collapse in OSA patients, with repetitive collapse occurring during both of these breathing processes. LAT may be an important anatomical factor associated with OSA pathogenesis and treatment.

Introduction

Obstructive sleep apnea (OSA) is a debilitating condition wherein the upper airway is repeatedly obstructed during sleep.[1] OSA patients often present with symptoms including decreased oxygen saturation, excessive daytime sleepiness, snoring, and certain long-term health outcomes including higher rates of cardiac disease, endocrine disease, circulatory disease, and mental illness.[2,3]

In prior studies, the 3D morphology of the upper airway has been evaluated via cephalometry, computed tomography (CT), and magnetic resonance imaging (MRI).[4] More recently, however, cone-beam computed tomography (CBCT) has emerged in the fields of dental and maxillofacial imaging owing to its lower cost and reduced radiation dosage.[5] CBCT has also been successfully leveraged to assess the 3D structure of the upper airway,[6–8] enabling the measurement of parameters including upper airway volume and minimum cross-sectional area.

Computational fluid dynamics (CFD) is an engineering tool that simulates the flow of gases or fluids flowing through a tube.[9] Given the irregular tubular structure of the upper airway, CFD can similarly be employed for quantitative analyses of airflow in the airways, allowing for the assessment of fluid dynamic parameters including velocity, pressure, and wall shear stress.[10,11]

By using CBCT to measure the 3D morphology of OSA patients and then analyzing the aerodynamic characteristics of their upper airways, it may be possible to better understand the mechanistic basis for airway obstruction in this pathological context. Two prior studies have compared upper airway aerodynamic characteristics in OSA patients and controls, but these studies were hampered either by their small size ($n = 8$ participants, including two with moderate OSA, two with severe OSA, and four controls)[12] or by a lack of any patients with severe OSA ($n = 31$, including 14 with mild-moderate OSA and 17 controls).[13] Given that severe OSA is a potentially lethal condition associated with serious long-term health outcomes, it is essential that more studies of individuals with this disease be conducted. As such, we herein compared the airway morphology of individuals with mild, moderate, and severe OSA in an analysis with a relatively large sample size.

Materials and methods

Patient selection

This retrospective analysis was approved by the Peking University School and Hospital of Stomatology Institutional Review Board (Approval Number: PKUSSIRB-202056092). 40 OSA patients (22 male, 18 female) included in this study were initially presented to Peking University School and Hospital of Stomatology from April 2015 to December 2019. Patients eligible for study inclusion were:[1] at least 18 years older;[2] diagnosed with OSA [apnea hypopnea index (AHI) $\geq$ 5];[3] associated with complete PSG and CBCT data for analysis. Patients were excluded if they:[1] were diagnosed with other respiratory or sleep disorders such as central sleep apnea syndrome or[2] exhibited reversible morphological upper airway abnormalities such as enlarged tonsils. Patients were stratified into three groups based upon their AHI scores (Table 1): a mild OSA group (5 males and 12 females; mean AHI, 9.1 $\pm$ 2.7 events/h; mean age, 26.4 $\pm$ 6.8 years; mean body mass index [BMI], 20.8 $\pm$ 1.7 kg/m^2); a moderate OSA group (nine males and two females; mean AHI, 22.4 $\pm$ 3.5 events/h; mean age, 30.0 $\pm$ 7.7 years; mean BMI, 22.3 $\pm$ 3.2 kg/m^2), and a severe OSA group (eight males and four females; mean AHI, 59.1 $\pm$ 14.1 events/h; mean age, 30.8 $\pm$ 10.2years; mean BMI, 20.9 $\pm$ 2.1 kg/m^2).

Polysomnography

Overnight PSG recordings (Philips Alice 6, Pittsburgh, PA, USA) were used to measure AHI values for all patients. Apnea was defined by a $\geq$90% disruption of airflow for a minimum of 10 s, while hypopnea was defined by a $>$30% airflow reduction for at least 10 s with a $>$4% oxygen desaturation. AHI was determined based upon the number of apnea and hypopnea events per hour during sleep.[14] Patient BMI and lowest oxygen saturation (LSAT) during the PSG study were also recorded.

CBCT imaging

CBCT analyses for all patients were conducted with the same instrumentation (Newtom5G, Verona, Italy) and the same exposure settings at 110 kV; 5 mA; 0.3 mm voxel size;

Table 1 Patient demographics and AHI parameters.

	Mild OSA (17)	Moderate OSA (11)	Severe OSA[12]
Age (years)	26.3 $\pm$ 6.8	30.0 $\pm$ 7.7	30.8 $\pm$ 10.2
Gender	70.6% (F)	18.2% (F)	33.3% (F)
BMI (kg/m^2)	20.8 $\pm$ 1.7	22.3 $\pm$ 3.2	20.9 $\pm$ 2.1
AHI (time/hour)	9.1 $\pm$ 2.7	22.4 $\pm$ 3.5	59.1 $\pm$ 14.1
LSAT (%)	90.1 $\pm$ 2.0	82.3 $\pm$ 2.8	69.6 $\pm$ 9.8

Note: BMI: body mass index, AHI: apnea hypopnea index, LSAT: the lowest oxygen saturation during PSG, OSA: obstructive sleep apnea.

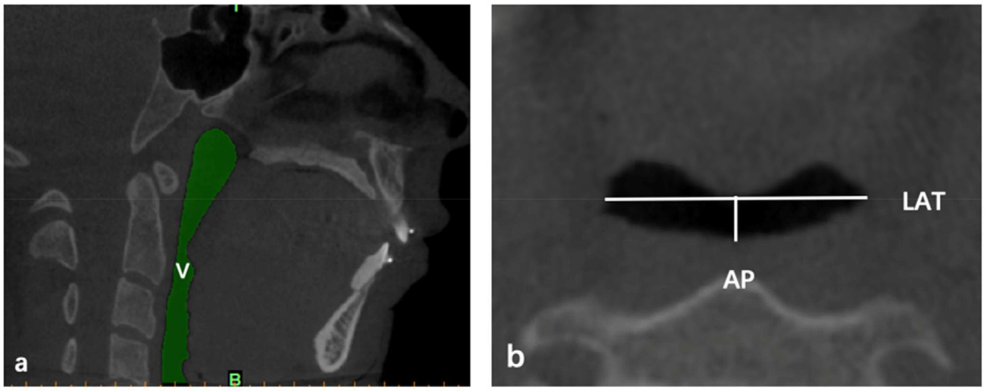

Figure 1 3D morphological characteristics of the upper airway in OSA patients. (a) The total volume of the upper airway (V), (b) The minimum axial area (MMA) of the upper airway. AP, the anteroposterior dimension of the MMA; LAT, the lateral dimension of the MMA. Note: OSA: obstructive sleep apnea, V: volume of the upper airway, MMA: minimum axial area, AP: anteroposterior dimension of MMA, LAT: lateral dimension of MMA.

rotation time of 8.9 s. For CBCT scans, patients were seated with natural head posture and were instructed not to move or swallow during imaging, breathing quietly and maintaining centric occlusion with a relaxed tongue and lips. Digital Imaging and Communication in Medicine (DICOM) files were used to store and analyze scan data.

Assessment of upper airway morphology

The upper airway morphology of OSA patients was assessed with the Mimics 17.0 (Materialise Inc, Leuven, Belgium) software, which was used for airway segmentation and 3D modeling.[15] Briefly, DICOM files were first adjusted to a standard head orientation, with the Frankfort horizontal (FH) plane serving as a reference plane parallel to the global horizontal plane. While in a frontal view orientation, the right and left frontozygomatic sutures were marked with the Mimics software, and the patient's median line was aligned with that displayed in the software program. A new mask was then created with thresholds from −1024 to −579, after which the superior boundary (the plane across the top of the nasopharynx parallel to the FH plane), inferior boundary (the plane across the base of the epiglottis parallel to the FH plane), anterior boundary (the coronal plane across the posterior nasal spine), and posterior boundary (the posterior pharyngeal wall) were selected.[16] The upper airway total volume (V), the minimum axial area (MMA), the anteroposterior dimension of the MMA (AP), and the lateral dimension of the MMA (LAT) were then established (Fig. 1).

Evaluation of upper airway aerodynamics

Fluid dynamic properties of patient airways were assessed by importing 3D surface mesh models of the airways into ANSYS Fluent 18.1 (ANSYS Inc, Canonsburg, PA, USA) in the form of STL files that could be used for upper airway flow simulations. These investigations were conducted using unsteady Reynolds-averaged Navier—Stokes (RANS) models with a low Reynolds number K-ω turbulence model.[17] Air compressibility can be neglected in these analyses given that air velocity is less than Mach 0.2 in the airways, and upper airway airflow was considered to be adiabatic. Second-order discretization schemes were used for pressure and momentum equations. Pressure-velocity coupling was assessed with the SIMPLE scheme,[18] and spatial discretization was achieved via a least-squares cell-based gradient approach with the boundary condition being set to the axial velocity at the inlet plane, where the pressure was set to 1 atm, and a no-slip condition was imposed for the upper airway wall. The volume flow rate of the inlet boundary was set to 250 ml/s during simulations, while the viscosity and density of air were set to 1.79×10^{-5} kg/m/s and 1.225 kg/m^3, respectively.[13] Inspiration was simulated by setting the inlet plane at the coronal plane across PNS with the outlet at the base of the epiglottis, whereas expiration was simulated by reversing this arrangement. The pressure at the outlet boundary was set at 0 atm. All simulations and associated calculations were made under the same conditions. Contours of velocity (m/s), wall shear stress (Pa), and wall static pressure (Pa) for a representative OSA patient during inspiration and expiration are shown in Fig. 2.

Computational fluid dynamics outcome parameters

The ANSYS software was used to calculate velocity, wall shear stress, and wall static pressure during inspiration and expiration. Airway resistance (R) was determined as follows:

$$R = \Delta P/Q$$

Where ΔP was the total pressure drop between the inlet and outlet boundaries of the upper airway, and Q was the volume flow rate in the upper airway.

Statistical analyses

SPSS v24.0 (IBM, Armonk, NY, USA) was used to all statistical testing. Patients were stratified according to their AHI values. Data normality was assessed via the Shapiro—Wilk W

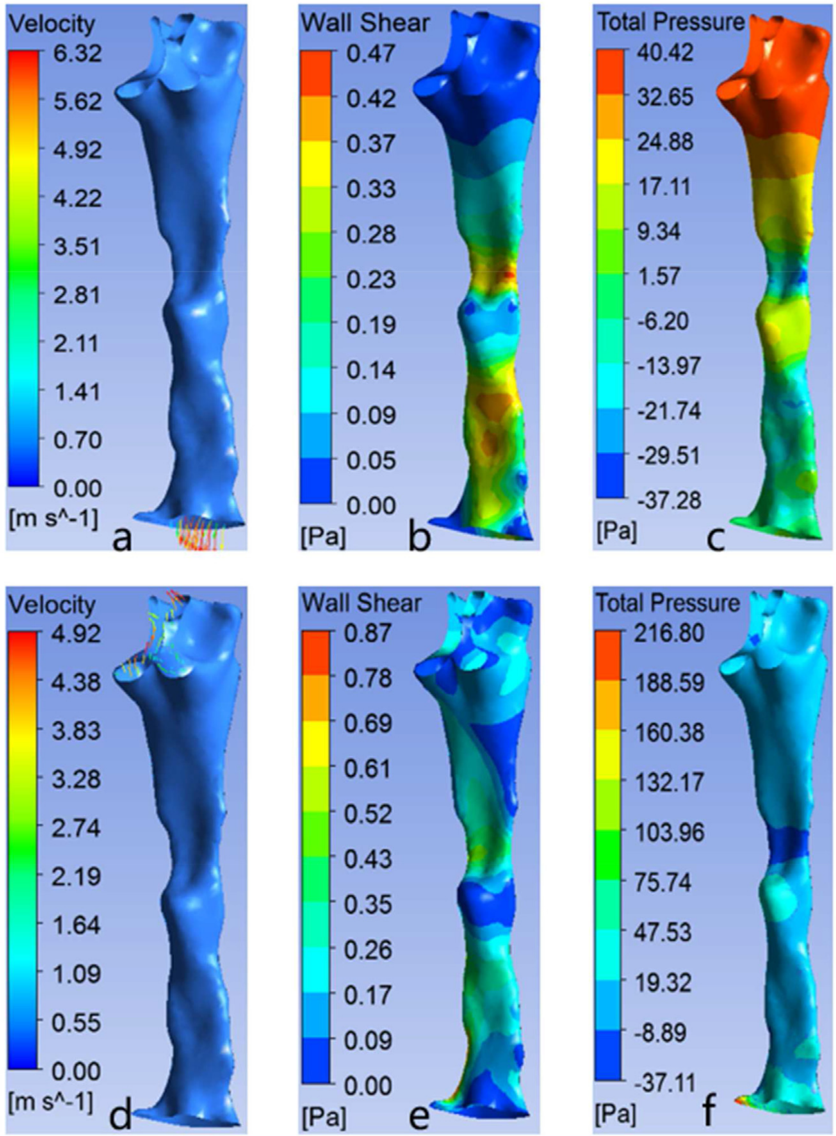

Figure 2 Aerodynamic characteristics of the upper airway in OSA patients. (a) Velocity (m/s) contours in a patient with severe OSA during inspiration, (b) Wall shear stress (Pa) contours in a patient with severe OSA during inspiration, (c) Wall static pressure (Total pressure) (Pa) contours in a patient with severe OSA during inspiration, (d) Velocity (m/s) contours in a patient with severe OSA during expiration, (e) Wall shear stress (Pa) contours in a patient with severe OSA during expiration, (f) Wall static pressure (Total pressure) (Pa) contours in a patient with severe OSA during expiration. *Note: OSA: obstructive sleep apnea.*

Test. Pearson's correlation analyses and one-way ANOVAs were used to assess relationships between OSA severity (AHI), BMI, LSAT, CFD parameters, and geometric parameters. Non-normally distributed data were assessed via the Kruskal—Wallis test and Spearman's correlation analyses. $P < 0.05$ was the significance threshold.

Results

Patient demographic and clinical characteristics

In total, 40 patients were assessed in this retrospective study, and were stratified into three groups of those with mild OSA ($5 < \text{AHI} \leq 15$), moderate OSA ($15 < \text{AHI} \leq 30$), and severe OSA ($\text{AHI} > 30$). Patient demographics are compiled in Table 1. There were no significant differences in patient age or BMI among these groups, although gender did vary significantly between groups, with females accounting for 70.6% of patients with mild OSA. This may be attributable to the fact that treatment in mild OSA patients primarily serves to correct dental and maxillofacial deformities.

Patient upper airway 3D morphological parameters are shown in Table 2. Significant differences in upper airway volume (V), minimum axial area (MMA), AP, and LAT were detected when comparing patients with severe OSA to all other patients. Specifically, severe OSA patients had a significantly smaller upper airway volume (15207.22 ± 5463.64 mm^3), MMA (42.79 ± 35.68 mm^2), AP (3.20 ± 1.72 mm), and LAT (13.62 ± 5.95 mm) values relative

Table 2 3D morphological characteristics of the upper airway in OSA patients.

	Mild OSA	Moderate OSA	Severe OSA	*P*
V (mm^3)	26833.21 ± 9150.10	24376.99 ± 6812.91	15207.22 ± 5463.64[a,b]	0.001**
MMA (mm^2)	147.92 ± 107.58	106.99 ± 56.01	42.79 ± 35.68[a,b]	<0.001**
AP (mm)	5.80 ± 3.55	5.45 ± 1.85	3.20 ± 1.72[a,b]	0.019*
LAT (mm)	25.78 ± 7.49	21.64 ± 6.46	13.62 ± 5.95[a,b]	<0.001**

Note: V: volume of the upper airway, MMA: minimum axial area, AP: anteroposterior dimension of MMA, LAT: lateral dimension of MMA. OSA: obstructive sleep apnea.
[a] $P < 0.05$: compared with mild OSA group.
[b] $P < 0.05$: compared with moderate OSA group. *$P < 0.05$, **$P < 0.01$.

Table 3 aerodynamic characteristics of the upper airway in OSA patients.

	Mild OSA	Moderate OSA	Severe OSA	*P*
Maximum velocity during inspiration (m/s)	2.08 ± 1.06	1.88 ± 0.70	3.72 ± 1.98[b]	0.002**
Maximum wall shear stress during inspiration (Pa)	0.06 ± 0.47	0.06 ± 0.03	0.28 ± 0.22[a,b]	<0.001**
Maximum wall static pressure during inspiration (Pa)	4.78 ± 3.73	4.65 ± 3.02	21.3 ± 18.11[a,b]	0.002**
Rin (Pa/L/min)	0.72 ± 0.56	0.78 ± 0.45	3.09 ± 2.39[a,b]	<0.001**
Maximum velocity during expiration (m/s)	2.80 ± 1.68	3.42 ± 1.33	8.57 ± 6.09[a]	0.004**
Maximum wall shear stress during expiration (Pa)	0.06 ± 0.06	0.07 ± 0.05	0.61 ± 0.95[a]	0.002*
Maximum wall static pressure during expiration (Pa)	6.79 ± 7.34	6.96 ± 5.71	57.05 ± 80.60[a]	0.008**
Rex (Pa/L/min)	0.72 ± 0.73	0.86 ± 0.63	6.79 ± 8.73[a]	0.002**

Note: Rin: resistance during inspiration, Rex: resistance during expiration, OSA: obstructive sleep apnea.
[a] $P < 0.05$: compared with mild OSA group.
[b] $P < 0.05$: compared with moderate OSA group. *$P < 0.05$, **$P < 0.01$.

to patients with moderate or mild disease. However, there was no significant difference between patients with mild and severe OSA in these 3D morphological parameters.

Patient upper airway aerodynamic characteristics are displayed in Table 3. We observed significant differences in maximum velocity, maximum wall shear stress, maximum wall static pressure, and resistance during both inspiration and expiration among patients with differing levels of disease severity. In inspiration phase, those with severe OSA exhibited significantly higher maximum wall shear stress (0.28 ± 0.22 Pa), maximum wall static pressure (21.3 ± 18.11 Pa), and resistance (3.09 ± 2.39 Pa/L/min) than did patients in the other two groups, but only exhibited a significantly faster maximum velocity (3.72 ± 1.98 m/s) than did patients with moderate OSA. In expiratory phase, those with severe OSA only exhibited higher maximum velocity (8.57 ± 6.09 m/s), maximum wall shear stress (0.61 ± 0.95 Pa), maximum wall static pressure (57.05 ± 80.60 Pa), and resistance (6.79 ± 8.73 Pa/L/min) than did patients with mild OSA. Patients with severe OSA showed more typical aerodynamic characteristics compared with the other two groups, and were more significant in inspiratory phase. In contrast, these parameters did not differ significantly between patients with mild and moderate OSA.

Correlation between resistance and upper airway anatomical characteristics in analyzed OSA patients are shown in Table 4 (inspiration) and Table 5 (expiration). Patients with mild OSA, resistance during inspiration (Rin) was significantly negatively correlated with volume of the upper airway (V) ($r = -0.510$, $P = 0.037$), minimum axial area (MMA) ($r = -0.706$, $P = 0.002$), and lateral dimension of MMA (LAT) ($r = -0.678$, $P = 0.003$) during inspiration (Fig. 3a, b, 3c). Resistance during expiration (Rex) was

Table 4 Correlation between airway resistance during inspiration (Rin) and the upper airway characteristics.

	Mild OSA		Moderate OSA		Severe OSA	
	r	*P*	*r*	*P*	*r*	*P*
V (mm^3)	−0.510	0.037*	−0.600	0.051	−0.693	0.013*
MMA (mm^2)	−0.706	0.002**	−0.698	0.017*	−0.685	0.014*
AP (mm)	−0.343	0.178	−0.538	0.088	−0.483	0.112
LAT (mm)	−0.678	0.003**	−0.709	0.015*	−0.724	0.008**

Note: V: volume of the upper airway, MMA: minimum axial area, AP: anteroposterior dimension of MMA, LAT: lateral dimension of MMA. OSA: obstructive sleep apnea. *$P < 0.05$, **$P < 0.01$.

Table 5 Correlation between airway resistance during expiration (Rex) and the upper airway characteristics.

	Mild OSA		Moderate OSA		Severe OSA	
	r	*P*	*r*	*P*	*r*	*P*
V (mm^3)	−0.417	0.096	−0.721	0.012*	−0.692	0.013*
MMA (mm^2)	−0.563	0.019*	−0.657	0.028*	−0.909	<0.001**
AP (mm)	−0.269	0.297	−0.456	0.158	−0.797	0.002**
LAT (mm)	−0.517	0.033*	−0.652	0.030*	−0.923	<0.001**

Note: V: volume of the upper airway, MMA: minimum axial area, AP: anteroposterior dimension of MMA, LAT: lateral dimension of MMA. OSA: obstructive sleep apnea. *$P < 0.05$, **$P < 0.01$.

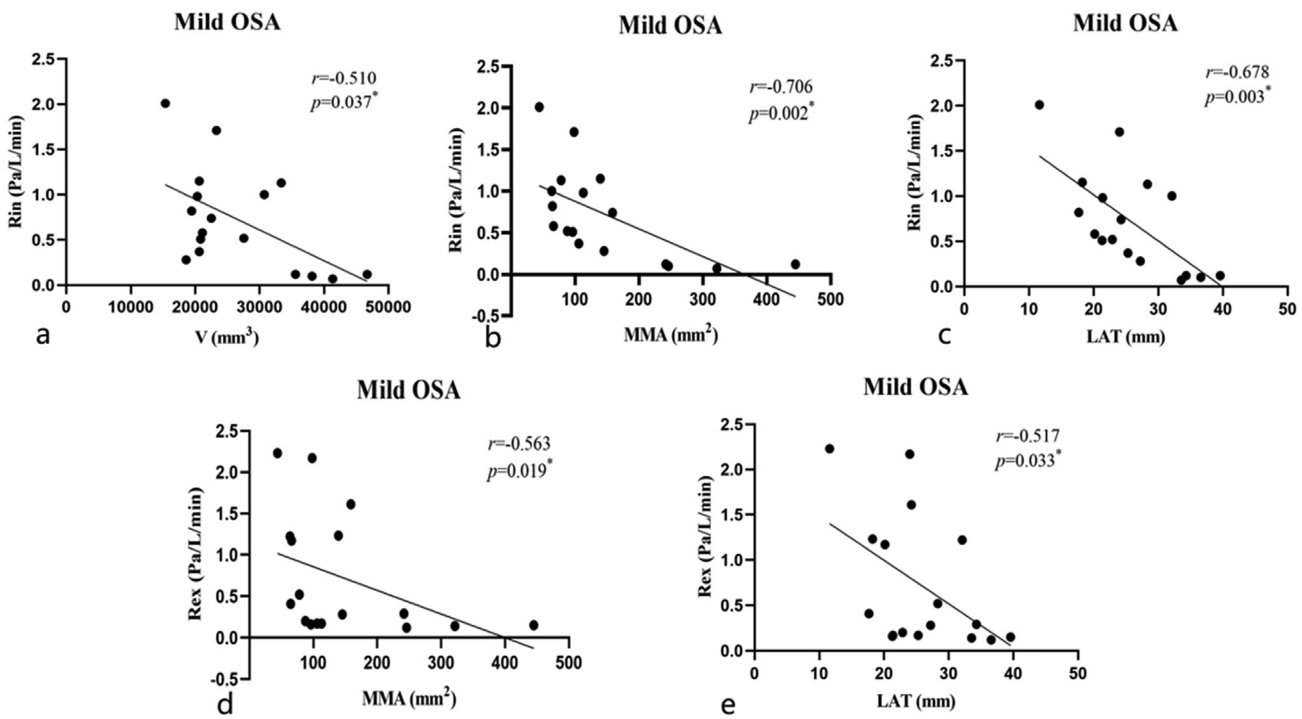

Figure 3 Correlations between airway resistance and 3D morphological parameters in mild OSA patients. (a) Rin and V, (b) Rin and MMA, (c) Rin and LAT, (d) Rex and MMA, (e) Rex and LAT. *Note: OSA: obstructive sleep apnea, Rin: resistance during inspiration, Rex: resistance during expiration, V: volume of the upper airway, MMA: minimum axial area, LAT: lateral dimension of MMA.*

significantly negatively correlated with MMA ($r = -0.563$, $P = 0.019$), LAT ($r = -0.517$, $P = 0.033$) during expiration (Fig. 3d and e). Patients with moderate OSA, Rin was significantly negatively correlated with MMA ($r = -0.698$, $P = 0.017$) and LAT ($r = -0.709$, $P = 0.015$) during inspiration (Fig. 4a and b). Rex was significantly negatively correlated with V ($r = -0.721$, $P = 0.012$), MMA ($r = -0.657$, $P = 0.028$) and LAT ($r = -0.652$, $P = 0.030$) during expiration (Fig. 4c, d, 4e). Patients with severe OSA, Rin was significantly negatively correlated with V ($r = -0.693$, $P = 0.013$), MMA ($r = -0.685$, $P = 0.014$) and LAT ($r = -0.724$, $P = 0.008$) during inspiration (Fig. 5a, b, 5c). Rex was significantly negatively correlated with V ($r = -0.692$, $P = 0.013$), MMA ($r = -0.909$, $P < 0.001$), LAT ($r = -0.923$, $P < 0.001$) and anteroposterior dimension of MMA (AP) ($r = -0.797$, $P = 0.002$) during expiration (Fig. 5d, e, f, g). MMA and LAT these two parameters showed significantly negatively correlated with resistance during inspiration and expiration in three groups. AP was significantly negatively correlated with Rex only in severe OSA patients. 3D morphological parameters exhibited different correlations with aerodynamic parameters in three groups.

Discussion

Herein, we utilized CBCT images to evaluate the aerodynamic and morphological properties of the upper airways in a relatively large cohort of OSA patients.

CFD offers a means of directly assessing the upper airway that can be leveraged by surgeons when planning treatments for this tissue site. While prior studies have utilized CFD-based approaches to assess the upper airways of OSA patients,[13,19,20] these studies have been limited by small sample sizes and a lack of patients with severe disease. Given that severe OSA patients exhibit distinct upper airway aerodynamic characteristics relative to those of patients with mild (n = 17) and moderate (n = 12) disease, it is important that such patients be analyzed in studies with a larger sample size (n = 11). We found severe OSA patients to exhibit certain distinctive morphological and aerodynamic characteristics in their upper airways relative to individuals with mild or moderate disease, including narrower airways, faster airflow velocity, higher static pressure, and increased shear stress and airway resistance. In contrast, these parameters did not differ significantly between individuals with mild or moderate OSA. This may suggest that severe OSA has a more complex pathogenesis that may be more challenging to treat, although more research is necessary to test this possibility.

Computational fluid dynamics simulations conducted herein revealed consistent patterns in those with both mild and severe OSA, with Rin being negatively correlated with upper airway volume, MMA, and LAT. In contrast, Rex was only significantly negatively correlated with LAT in these patients. In contrast, in those with moderate OSA, Rin was negatively correlated with MMA and LAT, while Rex was negatively correlated with upper airway volume, MMA, and LAT. These differences may be associated with the complex structures present in OSA patients, as the exact pathophysiology of this disease remains poorly understood.[21] Whether moderate OSA patients exhibit more complex upper airway structures remains to be investigated. In addition, no

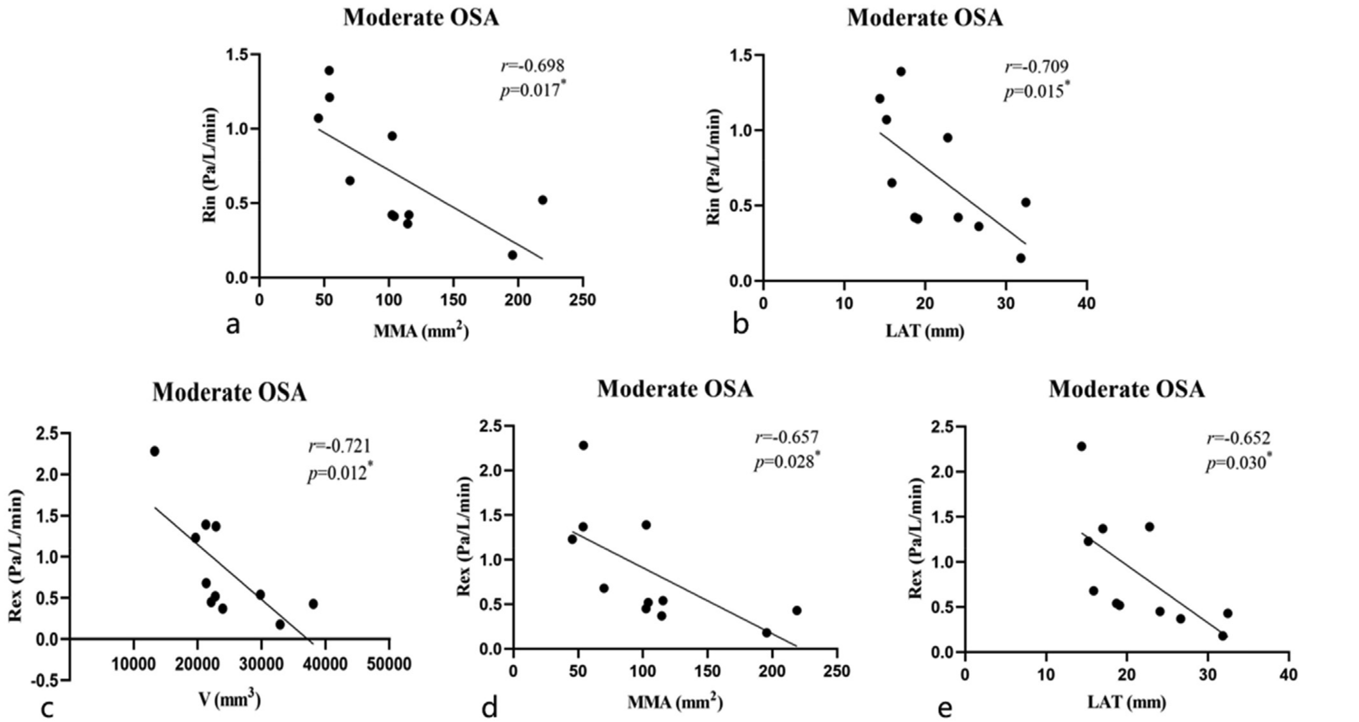

Figure 4 Correlations between airway resistance and 3D morphological parameters in moderate OSA patients. (a) Rin and MMA, (b) Rin and LAT, (c) Rex and V, (d) Rex and MMA, (e) Rex and LAT. *Note: OSA: obstructive sleep apnea, Rin: resistance during inspiration, Rex: resistance during expiration, V: volume of the upper airway, MMA: minimum axial area, LAT: lateral dimension of MMA.*

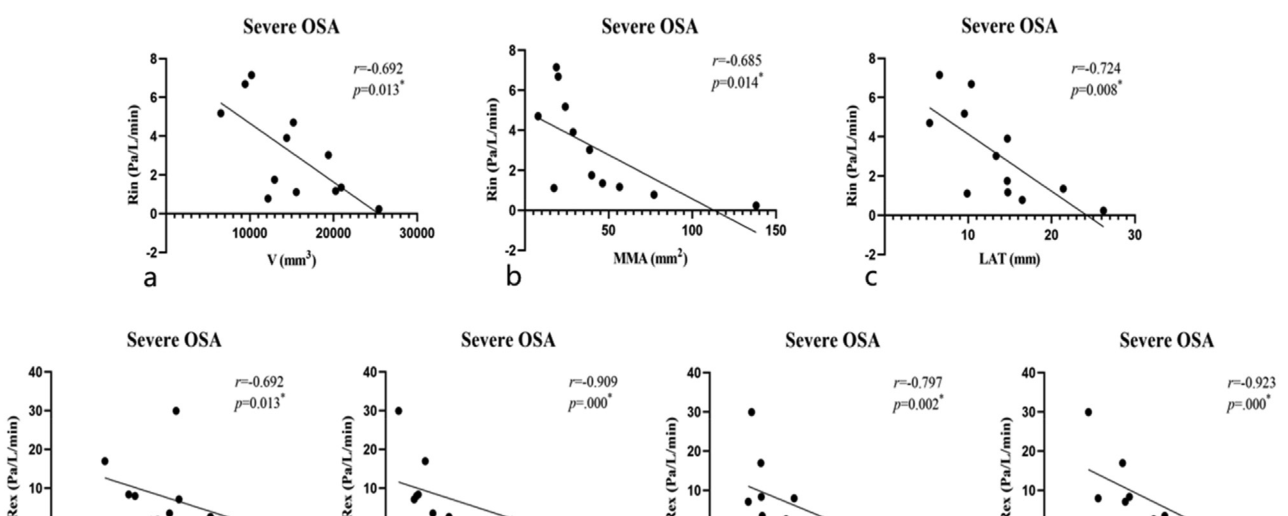

Figure 5 Correlations between airway resistance and 3D morphological parameters in severe OSA patients. (a) Rin and V, (b) Rin and MMA, (c) Rin and LAT, (d) Rex and V, (e) Rex and MMA, (f) Rex and AP, (g) Rex and LAT. *Note: OSA: obstructive sleep apnea, Rin: resistance during inspiration, Rex: resistance during expiration, V: volume of the upper airway, MMA: minimum axial area, LAT: lateral dimension of MMA, AP: anteroposterior dimension of MMA.*

consistent conclusions have been drawn regarding when upper airway collapse occurs during inspiration[20,22] or expiration.[13,23] Our aerodynamic parameter comparisons suggested Rin and Rex to be significantly correlated with upper airway morphological characteristics, indicating that these factors are most closely associated with repetitive upper airway collapse in individuals suffering from OSA. Chen et al. previously found OSA patient airway resistance to be higher than that in controls during expiration.[13] In that study, 31 patients with mild and moderate OSA were included, but no individuals with severe disease were analyzed. However, those with severe OSA face a higher risk of potentially fatal or debilitating outcomes, and it is vital that the mechanistic basis for upper airway collapse in these patients be understood so that their disease can be appropriately managed. Schwab et al. found that events during the later phases of expiration may play serve as key determinants of apnea.[23] However, Suga et al. observed ventilatory impairment at inspiration in OSA patients.[10] As such, there are no consistent conclusions regarding the timing of upper airway collapse in individuals suffering from this disease. Our results suggest that upper airway collapse may occur during both inspiration and expiration. Upper airway LAT and MMA exhibited significant correlations with Rin and Rex in all analyzed OSA patient groups, suggesting that LAT and MMA are the best anatomic parameters for use when predicting changes in upper airway resistance. Prior research has suggested that MMA may be a key determinant of flow resistance and disease clinical severity.[13,19,24] However, no studies to our knowledge have identified any correlation between upper airway resistance and LAT in OSA patients. We therefore propose that LAT may be an important mediator of upper airway collapse and treatment approaches for OSA patients in clinical settings. Enciso et al. found that OSA presence and severity was related to the narrow lateral dimension of the airway.[25] We therefore hypothesize that the smaller LAT in OSA patients may result in higher upper airway Rin and Rex, thus increasing the risk of airway collapse during sleep. These findings provide a theoretical basis for the potential treatment of OSA patients via orthognathic surgery, and further research on this topic is warranted.

In conclusion, we found that patients suffering from severe OSA exhibited characteristic upper airway 3D morphological and aerodynamic findings, including higher shear stress, greater airway narrowing, faster airflow, and higher levels of static pressure and airway resistance. Airway resistance during inspiration and expiration were identified as the characteristics most closely associated with upper airway collapse, while LAT may be directly relevant to the pathogenesis and treatment of OSA patients. However, further large-scale prospective studies will be essential to validate and expand upon our results.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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