ORIGINAL ARTICLE

Aortic Root Diameter in Hypertensive Patients With Various Stages of Obstructive Sleep Apnea

Dian Wang,[1] Jian-Zhong Xu,[1] Yuan-Yuan Kang,[1] Wei Zhang,[1] Lei-Xiao Hu,[1] and Ji-Guang Wang[1,]

BACKGROUND
Obstructive sleep apnea (OSA) is a risk factor of several cardiovascular diseases. We investigated the association between aortic root diameter and hypoxia-related parameters in hypertensive patients with OSA.

METHODS
Our study included 242 hypertensive patients with OSA (52 mild, 71 moderate, and 119 severe). All the patients underwent echocardiography for measuring aortic root diameter and polysomnography for measuring apnea–hypopnea index (AHI), oxygen desaturation index, and time spent with oxygen desaturation less than 90%.

RESULTS
The study patients included 19.8% women and had a mean (±SD) age of 49.9 ± 12.9 years, a mean aortic root diameter of 33.4 ± 2.6 mm, and a prevalence of echocardiographic aortic root dilation of 3.7%. Patients with mild, moderate, and severe OSA had similar echocardiographic left ventricular structure. However, patients with severe OSA had a significantly ($P < 0.05$) greater aortic root diameter (33.9 ± 2.4 mm vs. 32.4 ± 2.2 and 33.4 ± 2.9 mm, respectively) and higher prevalence of aortic root dilatation (5% vs. 1% and 3%, respectively) than those with mild and moderate OSA. Aortic root diameter corrected by body height was significantly ($P < 0.001$) associated with AHI, oxygen desaturation index and time spent with oxygen desaturation less than 90% ($r = 0.23–0.33$). After adjustment for various confounding factors, the associations between aortic root diameter and polysomnography parameters remained statistically significant ($P < 0.05$).

CONCLUSIONS
The severity of OSA was associated with the aortic root diameter. Patients with severe OSA had a greater aortic root diameter.

Keywords: aortic root diameter; blood pressure; echocardiography; hypertension; obstructive sleep apnea.

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Obstructive sleep apnea (OSA) is disordered breathing in which the upper airway closes repeatedly during sleep.[1] These repetitive partial or complete cessations of airflow during sleep result in intermittent hypoxia and oxygen desaturation. Clinic-based observational studies have reported that OSA is associated with an increased risk of cardiovascular diseases, such as systemic arterial hypertension, coronary artery disease, congestive heart failure, cardiac arrhythmia, and stroke.[2–5]

Several previous studies showed that OSA also promoted progressive aortic dilatation in patients with Marfan's syndrome, aortic aneurysm, or aortic dissection.[6–8] An increased aortic root diameter represents a risk factor for left ventricular hypertrophy, left ventricular dysfunction, and renal dysfunction.[9–11] Several nonhemodynamic factors influence aortic root diameter, including age, gender, body height, cigarette smoking, blood pressure, serum lipids, and plasma glucose.[12–14]

We hypothesize that intermittent hypoxia as a prominent feature of OSA is associated with the changes in aortic root diameter. In the present study, we investigated the association between aortic root diameter and various hypoxia-related parameters, including apnea–hypopnea index (AHI), oxygen desaturation index, and time spent with oxygen desaturation less than 90% in patients with OSA.

METHODS

Study population

Our retrospective cross-sectional study included 242 adult hypertensive patients with a confirmed diagnosis of OSA,

Correspondence: Ji-Guang Wang (jiguangwang@aim.com).

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[1]The Shanghai Institute of Hypertension, Department of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

who admitted in the hypertension ward in Ruijin Hospital, Shanghai, China from May 2020 to April 2021. All these patients underwent full polysomnography due to symptoms of nocturnal snoring and/or excessive daytime sleepiness. According to the AHI, patients were classified as mild, moderate, and severe OSA with an AHI 5–15/hour (n = 52), 15–30/hour (n = 71), and ≥30/hour (n = 119), respectively.

Exclusion criteria included atrial fibrillation, respiratory failure, congestive heart failure, coronary artery disease, significant valvular heart disease, congenital heart disease, and suboptimal echocardiographic windows. The study protocol was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. All patients gave informed written consent.

Polysomnography

All patients underwent an overnight polysomnographic study using a standardized suite (Philips Respironics, Pittsburgh, PA). Sleep parameters were then recorded and analyzed. Experienced technicians identified the respiratory events according to the standard criteria. Apnea was defined as complete cessation of airflow for at least 10 seconds, and hypopnea was defined as a ≥50% reduction in airflow, lasting at least 10 seconds, associated with a decrease of at least 4% in the nocturnal oxygen saturation (SaO_2) or state of arousal. AHI was calculated as the total number of apneas and/or hypopneas per hour. OSA was defined as AHI ≥5 events per hour. Other sleep parameters included mean saturation of arterial oxygen (mean SaO_2), minimum saturation of arterial oxygen (minimal SaO_2), oxygen desaturation index, and cumulative time with SaO_2 <90%.

Echocardiography

Standard 2-dimensional (2D) echocardiography was performed at rest by an experienced research sonographer blinded to clinical information and respiratory data using the Philips IE33 device (Philips, Eindhoven, The Netherlands). Aortic root diameter was measured in the parasternal long-axis view at the level of sinus of Valsalva in end-diastole, using the leading-edge to leading-edge method.[15] The aortic root diameter corrected for body height was used for further statistical analysis.[16] Aortic root dilation was defined as an aortic root diameter greater than 37 mm for men and 34 mm for women.[17]

Left ventricular end-diastolic diameter (LVEDd), diastolic posterior wall thickness (PWTd), and diastolic interventricular septum thickness (IVSTd) were imaged from a parasternal long-axis window at the level of the mitral chords using 2D-targeted M-mode echocardiography. Left ventricular mass (LVM) was calculated according to the American Society of Echocardiography-cube formula by Devereux *et al.*: $\mathrm{LVM\ (g)} = 0.8 \times [1.04 \times \{(\mathrm{LVEDd} + \mathrm{PWTd} + \mathrm{IVSTd})3 - (\mathrm{LVEDd})3\}] + 0.6$. LVM was indexed for body surface area to obtain left ventricular mass index (LVMI). Left ventricular hypertrophy was defined as a LVMI >115 g/m^2 in men and >95 g/m^2 in women. We measured the peak velocities of early (E) and atrial (A) diastolic filling, mitral valve deceleration time, and isovolumic relaxation time and calculated the E/A ratio. E′ was the mean value of the mitral annular velocities measured at the septal and lateral annuli by tissue Doppler imaging. The E/E′ ratio was calculated by dividing early mitral inflow velocity (E) by early diastolic mitral annular velocity (E′).

Blood pressure measurement

Blood pressure was measured on the day of admission at the hypertension inpatient ward. An automated oscillometric electronic blood pressure monitor was used during the entire study period (Omron BP-1300, Omron Healthcare, Kyoto, Japan). Two consecutive readings were obtained with a 1-minute interval after at least 5 minutes rest in the seated position. These 2 blood pressure readings were averaged for statistical analysis.

Ambulatory blood pressure monitoring was performed during hospitalization. We programmed validated oscillometric SpaceLabs 90217 monitors (SpaceLabs, Redmond, WA) to obtain blood pressure readings at 20-minute intervals during daytime (06:00–22:00) and at 30-minute intervals during nighttime (22:00–06:00). All recordings covered >20 hours and included ≥10 readings during the awake period and ≥5 readings during sleep. Mean values were weighed for the time interval between consecutive readings.

Statistical analysis

Statistical analysis was performed using the SPSS software, version 17.0 (SPSS, Chicago, IL). Continuous variables were expressed as mean ± SD and nominal variables as percentages. Analysis of covariance was performed for the between-group comparisons. Correlation analysis was performed to study the associations of interest. While the main analysis focused on the aortic root diameter corrected by body height, we performed sensitivity analysis with the aortic root diameter corrected by body surface area. P values <0.05 were considered to be statistically significant.

RESULTS

Patient characteristics

Clinical characteristics of the patients according to the severity of OSA are shown in Table 1. Patients with severe OSA had a significantly ($P \leq 0.002$) greater body weight and body mass index and higher 24-hour, daytime, and nighttime ambulatory diastolic blood pressure than patients with mild and moderate OSA. They had similar age, sex, body height, clinic blood pressure, clinic pulse rate, 24-hour, daytime, and nighttime ambulatory systolic blood pressure, 24-hour pulse rate, hypertension history, prevalence of diabetes mellitus, dyslipidemia, and current smoking ($P \geq 0.07$), but significantly different use of various classes of antihypertensive drugs ($P < 0.05$), except for calcium-channel blockers ($P = 0.44$) and diuretics ($P = 0.38$).

Polysomnography

The polysomnographic data are shown in Table 2. Patients with severe OSA, compared with those with mild or

moderate OSA, had a significantly higher AHI, time spent with oxygen desaturation <90% and oxygen desaturation index, and had a lower level of the mean nocturnal saturation of arterial oxygen, and the lowest saturation of arterial oxygen (all $P < 0.001$).

Standard echocardiography

The standard echocardiographic data are shown in Table 3. These patients had similar left ventricular diastolic and systolic diameter, interventricular septal wall thickness, left ventricular posterior wall thickness, shortening fraction, and ejection fraction, E/A, E/E′, LVM, LVMI, and prevalence of left ventricular hypertrophy and aortic root dilatation ($P \geq 0.24$). However, they had significantly different aortic root diameter corrected for body height (19.0 ± 1.3, 19.5 ± 1.6, and 19.8 ± 1.3 mm/m in patients with mild, moderate, and severe OSA, respectively, $P = 0.004$).

Correlation analyses between aortic root diameter corrected by body height and hypoxia-related parameters

Aortic root diameter corrected by body height was significantly ($P < 0.001$) associated with AHI, oxygen desaturation index and time spent with oxygen desaturation less than 90% (r = 0.23–0.33, with a progressive increase associated with the severity of OSA, Figures 1–3). After adjustment for age, gender, body mass index, LVMI, blood pressure, hypertension history, diabetes mellitus, dyslipidemia, current smoking, and use of antihypertensive medications, the associations between aortic root diameter and polysomnography parameters remained statistically significant ($P < 0.05$).

Table 1. Clinical characteristics of the study patients

Characteristic	Mild OSA (*n* = 52)	Moderate OSA (*n* = 71)	Severe OSA (*n* = 119)	*P* (ANOVA)
Age (y)	49 ± 13	51 ± 13	49 ± 12	0.61
Men (%)	73%	80%	83%	0.31
Body height (cm)	169 ± 7	171 ± 8	171 ± 8	0.33
Body weight (kg)	78 ± 12	81 ± 14	85 ± 14*,†	0.002
Body mass index (kg/m^2)	27 ± 3	27 ± 3	29 ± 3*,†	<0.001
Hypertension history (y)	7 ± 7	9 ± 10	10 ± 9	0.31
Clinic blood pressure (mm Hg)				
Systolic	148 ± 20	149 ± 21	147 ± 18	0.90
Diastolic	84 ± 9	87 ± 11	89 ± 13	0.07
Clinic pulse rate (beats/min)	80 ± 13	83 ± 11	82 ± 11	0.34
Ambulatory blood pressure (mm Hg)				
24-Hour systolic	136 ± 13	137 ± 14	138 ± 13	0.51
24-Hour diastolic	81 ± 9	85 ± 9	87 ± 14*	0.02
Daytime systolic	139 ± 13	140 ± 14	141 ± 13	0.52
Daytime diastolic	83 ± 9	87 ± 9*	90 ± 10*	0.001
Nighttime systolic	128 ± 17	128 ± 18	132 ± 16	0.32
Nighttime diastolic	77 ± 9	79 ± 11	83 ± 12*,†	0.004
24-Hour pulse rate (beats/min)	71 ± 9	72 ± 9	74 ± 10	0.23
Diabetes mellitus, *n* (%)	12 (23%)	16 (22%)	21 (17%)	0.74
Dyslipidemia, *n* (%)	8 (15%)	6 (23%)	29 (24%)	0.39
Current smoker, *n* (%)	14 (26%)	29 (40%)	39 (32%)	0.25
Use of antihypertensive drugs, *n* (%)				
Calcium-channel blockers	41 (78%)	62 (87%)	98 (82%)	0.44
Angiotensin-converting enzyme inhibitors	4 (8%)	20 (28%)	29 (24%)	0.02
Angiotensin receptor blockers	42 (80%)	37 (52%)	76 (58%)	0.005
β-Blockers	18 (34%)	22 (30%)	63 (52%)	0.005
α-Blockers	15 (28%)	26 (36%)	52 (44%)	0.05
Diuretics	14 (26%)	14 (19%)	34 (28%)	0.38

Values are mean ± SD. Abbreviations: ANOVA, analysis of variance; OSA, obstructive sleep apnea.
*$P < 0.05$ compared with mild obstructive sleep apnea.
†$P < 0.05$ compared with moderate obstructive sleep apnea.

Table 2. Polysomnography

Variable	Mild OSA (*n* = 52)	Moderate OSA (*n* = 71)	Severe OSA (*n* = 119)	*P* (ANOVA)
Apnea–hypopnea index (events/h)	9.5 ± 3.1	21.1 ± 4.1*	47.3 ± 14.2*,†	<0.001
Time spent with oxygen desaturation<90% (s)	6.5 ± 12.5	24.0 ± 61.0	74.7 ± 70.1*,†	<0.001
Mean oxygen saturation (%)	94 ± 1	93 ± 1	92 ± 2*,†	<0.001
Lowest oxygensaturation (%)	84 ± 5	81 ± 4*	71 ± 9*,†	<0.001
Oxygen desaturation index	10.2 ± 7.2	19.6 ± 8.9*	45.1 ± 17.6*,†	<0.001

Values are mean ± SD. Abbreviations: ANOVA, analysis of variance; OSA, obstructive sleep apnea.
*$P < 0.05$ compared with mild obstructive sleep apnea.
†$P < 0.05$ compared with moderate obstructive sleep apnea.

Table 3. Echocardiographic parameters

Variable	Mild OSA (*n* = 52)	Moderate OSA (*n* = 71)	Severe OSA (*n* = 119)	*P* (ANOVA)
Aortic root diameter (mm)	32.4 ± 2.2	33.4 ± 2.9*	33.9 ± 2.4*	0.002
Aortic root diameter corrected by body height (mm/m)	19.0 ± 1.3	19.5 ± 1.6*	19.8 ± 1.3*	0.004
Aortic root diameter corrected by body surface area (mm/m²)	17.3 ± 1.6	17.5 ± 1.8	17.2 ± 1.7	0.43
Aortic root dilation	1 (2%)	3 (4%)	6 (5%)	0.64
Left ventricular end-diastolic diameter (mm)	49.8 ± 3.9	50.1 ± 3.4	50.7 ± 3.4	0.26
Left ventricular end-systolic diameter (mm)	30.8 ± 4.1	31.5 ± 3.6	31.7 ± 3.2	0.35
Interventricular septal wall thickness (mm)	10.5 ± 1.9	10.8 ± 1.4	10.6 ± 1.4	0.72
Left ventricular posterior wall thickness (mm)	9.9 ± 1.4	10.2 ± 1.4	10.0 ± 1.2	0.50
Left ventricular shortening fraction (%)	38 ± 4	37 ± 4	37 ± 6	0.63
Left ventricular ejection fraction (%)	68 ± 6	67 ± 5	66 ± 4	0.38
E/A	1.02 ± 0.41	0.97 ± 0.35	0.95 ± 0.32	0.50
E/E′	10.2 ± 3.0	10.1 ± 2.6	10.4 ± 2.7	0.73
Left ventricular mass (g)	191.4 ± 53	198.8 ± 51.9	199.8 ± 50.6	0.60
Left ventricular mass index (g/m²)	101.3 ± 22.7	102.7 ± 20.1	100.3 ± 23.2	0.77
Prevalence of left ventricular hypertrophy (%)	13 (25%)	25 (35%)	29 (24%)	0.24

Values are mean ± SD. Abbreviations: ANOVA, analysis of variance; OSA, obstructive sleep apnea.
*$P < 0.05$ compared with mild obstructive sleep apnea.

Sensitivity analysis on aortic root diameter corrected by body surface area

Aortic root diameter corrected by body surface area was not significantly different (Table 3). However, both before and after adjustment for the aforementioned variables as appropriate, it was significantly associated with the polysomnography parameters ($P < 0.05$).

DISCUSSION

Our study showed that the severity of OSA was significantly associated with the aortic root diameter. Patients with severe OSA had a greater aortic root diameter. In fact, all major OSA-related parameters such as AHI, oxygen desaturation index and time spent with oxygen desaturation less than 90% were associated with the aortic root diameter in these hypertensive patients with various severities of OSA.

Our study was the first that investigated the relationship between aortic root diameter and various hypoxia-related parameters in hypertensive patients with OSA. Several previous studies showed that OSA promoted progressive aortic dilation in patients with Marfan's syndrome or aortic dissection.[18,19] Few studies investigated the association between OSA and aortic root diameter in patients without aortic diseases. In an early cross-sectional study in 76 patients with OSA, Meuleman *et al.* found that aortic root diameter ranged from 26.9 to 44.6 mm with a mean (±SD) of 35.3 ± 3.8 mm, and only 3 (3.9%) patients had aortic root dilation.[20] The investigators of the study concluded that the prevalence of aortic root enlargement was not increased in OSA[21] and reiterated in a published correspondence[22] on a research letter[23] that they did not find any correlation of aortic root diameter with AHI or time spent with oxygen desaturation less than 90%.[24] In the latter study in 150 consecutive patients who were referred for confirmation of OSA, thoracic aortic diameter measured with a chest CT was significantly greater in 110 patients with OSA than 40 patients without OSA ($n = 36.8 \pm 3.6$ mm vs. 31.5 ± 4.5 mm, $P < 0.001$).[22] Similarly, in 90 consecutive patients who were referred for the diagnosis of OSA, Cicek *et al.* found that patients with an AHI of 30 or higher ($n = 24$) had a

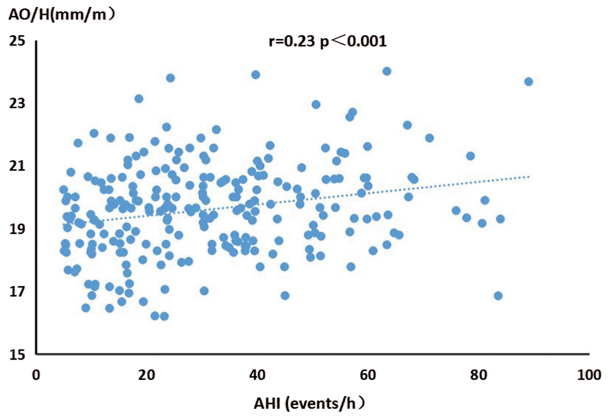

Figure 1. Correlation analyses between aortic root diameter corrected by body height (AO/H) and apnea–hypopnea index (AHI). Correlation coefficients and the corresponding *P* values are given.

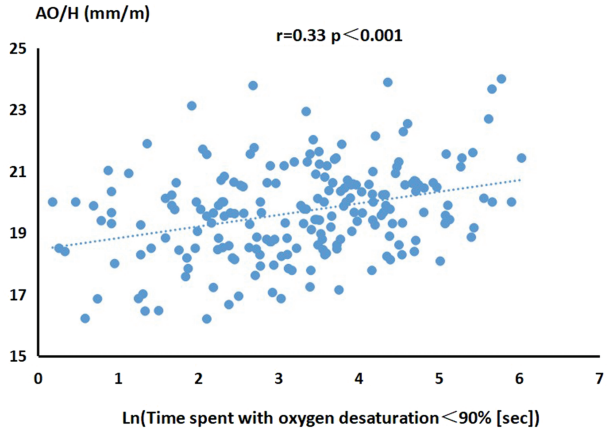

Figure 3. Correlation analyses between aortic root diameter corrected by body height (AO/H) and the logarithmically (Ln) transformed time spent with oxygen desaturation <90%. Correlation coefficients and the corresponding *P* values are given.

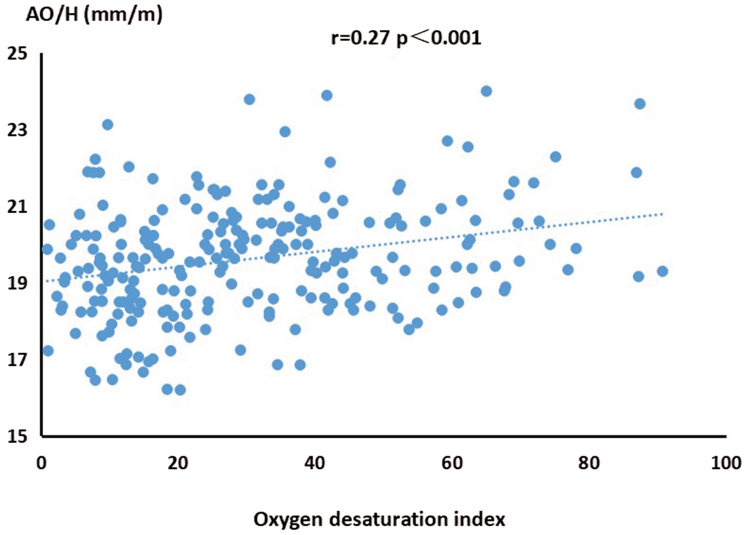

Figure 2. Correlation analyses between aortic root diameter corrected by body height (AO/H) and oxygen desaturation index. Correlation coefficients and the corresponding *P* values are given.

significantly greater aortic root diameter than those with an AHI below 30 (n = 66).[21] In a clinical experiment in 20 healthy subjects, Stöwhas *et al.* found that simulated hypopnea was associated with an increase in proximal aortic diameter.[25] In patients with both hypertension and OSA, our present study extends the findings of these previous studies by showing a significant association between aortic root diameter and various severity parameters of OSA.

OSA is a known independent risk factor of cardiovascular diseases. Our current study showed that OSA might also be a risk factor for aortic root dilatation. Aortic root dilatation is a risk factor for aortic dissection or rupture and a predictor of aortic valve regurgitation or even progression to aortic dissection. Lam *et al.* showed that aortic root dilation was associated with an increased risk of major adverse cardiovascular events and mortality.[26] As a noninvasive examination, echocardiography is useful in the early diagnosis of aortic root dilation.[27] The long axis of the left ventricle beside the sternum can show the structure of the aortic root. It can show the changes of the aortic structure and hemodynamics in the subclinical stage. In 2096 American patients with hypertension but without overt cardiovascular disease, Palmieri *et al.* found a 4.6% of prevalence of echocardiographic aortic root dilation, slightly higher than 3.7% of prevalence in our current study.[28]

The underlying mechanism for the association between severe OSA and increased aortic root diameter remains under investigation. It may involve intermittent hypoxia and reoxygenation, increased sympathetic nerve activity, and increased wall stress against intrathoracic organs induced by exaggerated negative intrathoracic pressure.[29,30] Time spent with oxygen desaturation less than 90% is a measure of the duration of hypoxia, and has been shown to be a better predictor of cardiovascular disease mortality than AHI.[31] Our study did show a slightly stronger association between this

measure and aortic root diameter, indicating a possible role of long lasting hypoxia and its consequences.

Why the aortic root diameter but not the measurements of cardiac structure and function differed between patients with severe, moderate, and mild OSA is not entirely understood. Our speculative explanation is that hypertension as a major cardiac risk factor must have played an important part. Our study patients had relatively severe hypertension. They had on average close to 10 years of hypertension history. Many of them were treated with combination antihypertensive therapy and still had inadequately controlled clinic and ambulatory blood pressure. Severe hypertension might to a large extent have accounted for the high proportion of left ventricular hypertrophy in our study participants. In fact, with regard to the association between OSA severity and cardiac structure and function, previous studies produced inconsistent results. Some,[32] but not other,[33,34] studies showed significant differences across various severity groups of OSA. The differences between these studies might have been confounded by patients characteristics, such as the prevalence, severity, and management of hypertension.

Our study has to be interpreted within the context of its limitations. First, aortic root is a complex structure including aortic anulus, aortic leaflets junction, aortic sinuses, and sinutubular junction. Measurement of aortic root diameter at sinuses of Valsalva is most commonly used, but may not be sufficiently accurate in assessing the aortic root diameter. A more comprehensive evaluation including additional measurements at various levels of annulus, supraaortic ridge, or proximal ascending aorta could help. Second, our study was retrospective, and lack of measurement of early cardiac dysfunction. Third, our study is cross-sectional and hence does not allow to draw any causal inference. Finally, our study participants had relatively smaller body mass index and lower prevalence of obesity than European and US patients with OSA.[23] The prevalence of obesity is increasing in China, but still relatively low. Indeed, according to the recent China nationwide blood pressure survey in 451,755 adults, mean body mass index was 23.8 kg/m^2 and 12.1% had a body mass index of ≥28 kg/m^2. Our study results should therefore cautiously extrapolated to obese populations.

In conclusion, the severity of OSA was associated with the aortic root diameter. Patients with severe OSA had a greater aortic root diameter. Future studies should address whether OSA is a causal risk factor for aortic root dilatation, and whether treatment of OSA such as the continuous positive airway pressure therapy would prevent aortic dilatation by correcting hypoxemia and negative intrathoracic pressures. If our finding is confirmed by these observational and interventional studies, a major implication would be that patients with severe OSA may need close monitoring on the changes in aortic root diameter and those with a fast increase in aortic root diameter may require intensive blood pressure control by the use of continuous positive airway pressure and antihypertensive drugs.

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DISCLOSURE

The authors declared no conflict of interest.

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