The Relative Impact of Obstructive Sleep Apnea and Hypertension on the Structural and Functional Changes of the Thoracic Aorta

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Background: Recent studies suggest that obstructive sleep apnea (OSA) causes thoracic aortic dilatation; but it is well accepted that hypertension can cause aortic dilatation, and hypertension is a common finding in patients with OSA. We aimed to investigate the relative impact of OSA and hypertension on the structural and functional changes of the thoracic aorta.

Methods: This was an echocardiography substudy of our prospective OSA study in patients with acute myocardial infarction (AMI). Ninety-four male patients who completed both echocardiography and polysomnography were recruited. OSA was defined as an apnea-hypopnea index (AHI) ≥ 15/hour.

Results: The patients' mean age was 53 ± 10 years, and mean body mass index (BMI) was 24.6 ± 3kg/m^2. Sixty-four (68.1%) patients had OSA; of these, 39 (41.5%) had severe OSA. Thirty-three (52.6%) of the OSA cohort had hypertension. There was no correlation between any of the echocardiographic parameters and thoracic aortic size. Stepwise multivariate regression showed that BMI (P = 0.024), older age (P = 0.044), and hypertension (P = 0.025) were the only determinants. There was no significant independent relationship between OSA/ AHI and thoracic aortic size. Systolic blood pressure but not AHI correlated significantly with aortic distensibility and compliance (r = −0.40 and −0.26, P < 0.001 and 0.022, respectively).

Conclusions: Hypertension is a common finding in male AMI patients with OSA. In these patients, increased afterload from systemic hypertension rather than mechanical stress on the aortic wall determines the thoracic aortic size and abnormalities in aortic functional indices. BMI and age were also independent predictors of thoracic aortic dilatation.

Keywords: Obstructive sleep apnea, hypertension, aortic root dilatation, acute myocardial infarction

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OBSTRUCTIVE SLEEP APNEA (OSA) IS WIDELY PREVALENT AMONG PATIENTS WITH CARDIOVASCULAR DISEASE, HYPERTENSION, DIABETES MELLITUS, and stroke.[1] It is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway resulting in interruption of airflow. The pathophysiological effect of OSA on the cardiovascular system is complex. Recurrent hypoxemia episodes caused by OSA heighten sympathetic drive, leading to increased endothelin production, which, in turn, leads to vasoconstriction.

Thoracic aortic dilatation is a potential predictor of subsequent aortic complication. Recent studies suggest that OSA causes thoracic aorta dilatation because of mechanical stress on the aortic wall from repeated episodes of apnea and hypopnea. However, these studies have not yielded consistent results.[2-4] Arterial stiffness has also been shown to be positively correlated with severity of OSA.[4,5] On the other hand, it is well accepted that hypertension can cause aortic dilatation; and hypertension is a common finding in patients with OSA.[3] We aimed to investigate the relative impact of OSA and hypertension on the structural and functional changes of the thoracic aorta.

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METHODS

Study Population

This study was an echocardiography substudy of our prospective OSA study involving 105 patients who were admitted to our institution for first acute ST elevation myocardial infarction from January 2007 to May 2008.[6] All patients underwent successful primary percutaneous coronary intervention (PCI). Exclusion criteria included known OSA, mechanical ventilation, cardiogenic shock, and inability to give informed consent. Ninety-four male patients (90%) who completed both echocardiography and polysomnography were included in our analysis. The study was approved by our institutional review board, and informed consents were obtained from all participants. Patient baseline demographic characteristics and cardiovascular risk factors were obtained during admission.

Echocardiography

Most of the patients (89%) underwent transthoracic echocardiography prior to discharge. In addition to routine echocardiographic parameters, the thoracic aortic dimension was recorded at the level of sinus of Valsalva, sinotubular junction, and proximal ascending aorta, defined as 3 cm above the aortic valve in the parasternal long axis view. Aortic systolic diameter was measured at the time of full opening of the aortic valve, and end diastolic diameter was measured at the onset of Q waves of the simultaneously recorded electrocardiogram (ECG).

All patients had blood pressure measured prior to echocardiographic assessment. Aortic distensibility and compliance were calculated. Aortic distensibility was defined as 2 × change

Table 1—Baseline patient characteristics

	Total (n = 94)	OSA (n = 64)	Without OSA (n = 30)	P
Age(year)	53 ± 10	54 ± 10	50 ± 9	NS
Male (%)	94 (100%)	64 (100%)	30 (100)%	NS
Race				
Chinese (%)	52 (55.3%)	36 (56.3%)	16 (53.3%)	NS
Malay (%)	21 (22.3%)	15 (23.4%)	6 (20.0%)	NS
Indian (%)	16 (17.0%)	10 (15.6%)	6 (2.0%)	NS
Others (%)	5 (5.3%)	3 (4.7%)	2 (6.7%)	NS
Body mass index (kg/m^2)	24.6 ± 3	24.9 ± 3	24.0 ± 3	NS
Hypertension	48 (51.1%)	33 (51.6%)	15 (50.0%)	NS
Hyperlipidemia	79 (84.0%)	54 (84.4%)	25 (83.3%)	NS
Smoker	57 (60.6%)	36 (56.3%)	21 (70.0%)	NS
Diabetes mellitus	37 (39.4%)	29 (45.3%)	8 (26.7%)	NS
Systolic blood pressure (mm Hg)	114 ± 17	117 ± 19	108 ± 12	0.020
Diastolic blood pressure (mm Hg)	68 ± 10	71 ± 11	65 ± 8	0.013
Anterior ST elevation myocardial infarction (%)	55 (57.9%)	35 (54.7%)	19 (63.3%)	NS
Peak creatinine kinase (U/L)	2749 ± 1923	2700 ± 1999	2936 ± 1746	NS
Peak creatinine kinase MB (mcg/L)	171 ± 98	163 ± 97	194 ± 95	NS
Antihypertensive medication use prior to admission	43 (45.7%)	30 (46.9%)	13 (43.3%)	NS

in diameter / [diastolic diameter × pulse pressure]; while aortic compliance was obtained by dividing the change in aortic area during systole and diastole (ΔA) by the pulse pressure. The measurement and calculation were done off-line by a single blinded investigator.

Polysomnography

Polysomnography was performed using a portable diagnostic device (Somte; Compumedics, Australia) between day 2 and 5 post-myocardial infarction. The parameters measured included nasal airflow (nasal cannula); thoracoabdominal movements (inductive respiratory bands); arterial oxygen saturation (pulse oximetry); snoring episodes (derived from the integrated pressure transducer); limb movement; ECG; and body position (continuous actigraphy).

The data were analyzed by 2 investigators without knowledge of the clinical characteristics of the patient. Apnea was defined as cessation of airflow > 10 sec; and hypopnea was defined as > 50% reduction of airflow lasting > 10 sec. An event was also considered to be hypopnea when there was a reduction in airflow that did not reach the 50% criterion, but was associated with arterial oxygen desaturation > 3%. The apnea-hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of recording time in bed. The patients were categorized by AHI score into OSA and non OSA. OSA was defined as AHI ≥ 15 events per hour; and severe OSA was defined as AHI > 30. Percentage of total sleep time during which oxygen saturation was less than 90% ($SatO_2$ < 90%) and 80% ($SatO_2$ < 80%) were also determined.

Statistical Analysis

All analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, Illinois). Paired 2-tailed Student *t*-test was used to compare the 2 groups. Correlations between variables were assessed with the Spearman correlation coefficient (r). Univariate associations between age, body mass index (BMI), AHI, hypertension, and thoracic aortic size were evaluated. Multiple regression analyses were then used to assess the independent determinants of thoracic aortic size, with correction for antihypertensive use prior to admission. Data are presented as mean ± standard deviation unless otherwise specified. P values less than 0.05 were considered significant (2-tailed).

RESULTS

Table 1 summarizes the clinical characteristics of the study cohort. The patients' mean age was 53 ± 10 years; mean BMI was 24.6 ± 3 kg/m^2. Sixty-four (68.1%) patients had OSA. Of these, 39 (41.5%) patients had severe OSA. Patients with OSA had higher blood pressure during transthoracic echocardiography than those without (P < 0.05). There was no difference in age, BMI, prevalence of diabetes, smoking, or hyperlipidemia between patients with OSA and those without OSA.

Patients with OSA had significantly greater thoracic aortic size than those without OSA (P < 0.05) (Table 2). A similar finding was noted in the hypertensive versus non-hypertensive patients (31.8 ± 3 mm versus 29.6 ± 3 mm, P = 0.001). The difference was especially marked between the normotensive non OSA patients and the hypertensive OSA patients, 28.5 ± 3 mm vs. 32.2 ± 3 mm (P = 0.002). We further subdivided the patients into subgroups based on severity of OSA (normal – AHI < 5; mild OSA – AHI 5-14; moderate OSA – AHI 14-29; severe OSA – AHI > 30) and found that compared with normals, patients with severe OSA had slightly larger thoracic aortic diameter (28.5 ± 3 mm vs 31.4 ± 3 mm, P = 0.048).

Patients with larger aortic root size were likely to be older, have a higher BMI, to be hypertensive, and to suffer from OSA. On univariate analysis, older age, BMI, AHI, and hypertension correlated positively with thoracic aortic size. Subsequent stepwise multivariate regression showed that BMI (P = 0.024), older age (P = 0.044), and hypertension (P = 0.025) were the only determinants. The percentage of total sleep time when oxygen saturation was less than 90% did not correlate with aortic size (r = 0.19, P = 0.70). There was also no correlation between any of the echocardiographic parameters and thoracic aortic size. BMI (P = 0.038) and older age (P = 0.018), but not OSA, remained independent predictors of greater thoracic aortic size after being corrected for antihypertensive medication use prior to admission (Table 3).

We found that resting systolic blood pressure, but not AHI, correlated strongly with aortic compliance (r = −0.26, P = 0.022) and aortic distensibility (r = −0.40, P < 0.001). Hypertensive patients with underlying OSA had the lowest compliance and

Table 2—Echocardiographic parameters of the patients

	OSA	Without OSA	P
Ejection fraction (%)	48 ± 12	48 ± 9	NS
Left ventricular mass index (g/m^2)	99 ± 27	105 ± 20	NS
Left atrium volume (mL)	38 ± 5	35 ± 5	NS
Mitral E	69.8 ± 18	70.8 ± 18	NS
Mitral A	63.6 ± 16	57.2 ± 13	NS
E/A	1.1 ± 0.4	1.3 ± 0.5	NS
Deceleration time (msec)	170 ± 40	171 ± 40	NS
PASP (mm Hg)	32 ± 11	30.8 ± 7	NS
Septal E'	7.5 ± 2	8.3 ± 2	NS
Septal A'	10.5 ± 2	10.0 ± 4	NS
Septal E'/A'	0.72 ± 0.2	0.90 ± 0.3	0.001
Septal E/E'	10.5 ± 7	8.7 ± 2	NS
Lateral E'	9.5 ± 3	10.3 ± 3	NS
Lateral A'	11.2 ± 3	10.5 ± 3	NS
Lateral E'/A'	0.88 ± 0.4	1.06 ± 0.5	NS
Lateral E/E'	8.2 ± 4	7.2 ± 2	NS
Aortic root diameter (mm)	31.2 ± 3.4	29.7 ± 3.0	0.047
Aortic root diameter/BMI	1.26 ± 0.2	1.25 ± 0.2	NS
Aortic root diameter/BSA	17.3 ± 2.1	16.9 ± 2.1	NS
Aortic distensibility (10^{-6}cm^2 dyn^{-1})	2.34 ± 1.32	2.89 ± 2.70	NS
Aortic compliance (mm^{2}mm Hg^{-1})	1.62 ± 0.79	2.00 ± 1.68	NS

Table 3—Multivariate predictors of aortic root dilatation after correction for antihypertensive use prior to admission

Variables	Standardized coefficients	95% Confidence Interval	P
BMI	0.214	0.014-0.480	0.038
Age	0.238	0.015-0.153	0.018
OSA	0.133	-0.381-2.281	NS

Table 4—Aortic elastic properties in different subgroups

	Aortic Elastic Properties	
Group	Compliance (mm^{2}mm Hg^{-1})	Distensibility (10^{-6}cm^2 dyn^{-1})
+Hypertension −OSA (n = 25)	1.71 ± 1.98	2.68 ± 1.14
+Hypertension +OSA (n = 29)	1.54 ± 0.82	2.05 ± 1.41
+OSA −Hypertension (n = 15)	2.10 ± 1.44	3.17 ± 2.95

P values were not significant between the groups.

distensibility values compared to OSA patients without hypertension or hypertensive patients without OSA (Table 4).

DISCUSSION

This study evaluated the relative impact of OSA and hypertension on the structural and functional changes of the thoracic aorta. We found that aortic root diameter was increased in patients with OSA and hypertension. Multivariate analysis, however, showed that only older age, BMI, and hypertension were independent predictors of greater thoracic aortic size. There was no significant independent relationship between OSA/AHI and thoracic aortic size. Additionally, systolic blood pressure, but not AHI, correlated significantly with aortic distensibility and compliance. Thus, in patients with OSA, increased afterload from systemic hypertension rather than mechanical stress on the aortic wall determines the thoracic aortic size and abnormalities in aortic functional indices. Age and BMI were also independent predictors of thoracic aortic dilatation.

Previous studies have shown that in patients with OSA, repetitive apneic episode results in repeated inspiratory effort against an occluded airway. Such repetitive inspiratory effort against an occluded airway can generate severe negative intrathoracic pressures, which can in turn affect intrathoracic hemodynamics. During each apneic episode, there is a marked increase in transmural pressure of the aortic wall, resulting in aortic dilatation.[1,7] An animal study showed that the intrathoracic aorta can be distended during diastolic phase in the setting of negative intrathoracic pressure, presumably due to diminished antegrade flow out of the thorax.[7] Furthermore, marked cyclical fluctuations in sympathetic activity and blood pressure, which have been shown to progressively increase during apneic episodes in patients with OSA, may also result in thoracic aortic dilatation. Even though these pathophysiological changes occur during sleep, it is believed that the hemodynamic and neurohumoral disturbances persist throughout 24 hours.[8] Hence, it is possible that the repetitive changes in intrathoracic pressure coupled with hemodynamic fluctuations in patients with OSA may result in thoracic aortic dilatation.[9] In addition, Cistulli et al showed that the rate of aortic dilatation was attenuated in OSA patients treated with nasal continuous positive airway pressure (CPAP).[10] In this study, we found that hypertension, but not OSA, was directly linked to aortic dilatation. The percentage of total sleep time when the oxygen saturation was less than 90% did not correlate with aortic size. Thus, the mechanical effect of OSA on the thoracic aorta probably does not translate to thoracic aortic dilatation. Although Cistulli and others[10-12] have shown reduction of blood pressure with CPAP use, there are marked differences in severity of OSA in different treatment trials and in inclusion/exclusion criteria.[13]

It is well accepted that hypertension can cause thoracic aortic dilatation. Increased afterload, impaired nitric oxide mediated vasodilatation, and prolonged vasoconstriction by endothelium-derived vasoconstrictors are some of the mechanisms that promote vascular remodelling and hypertrophy in hypertensive patients. Hypertension is a common finding in patients with OSA. Sixty-seven percent of our hypertensive cohort suffered from OSA. In fact, numerous epidemiological and animal studies have shown that OSA leads to hypertension.[13-15] Our findings suggested that in patients with OSA, increased afterload from systemic hypertension rather than changes in intrathoracic

hemodynamics caused by repetitive inspiratory effort against closed upper airway determines the thoracic aortic size.

Age and BMI were the other independent determinants of thoracic aortic size. Previous studies have demonstrated the relationship between thoracic aortic size and BMI. On the other hand, the relationship between age and thoracic aortic size is still controversial; studies to date have yielded conflicting results.[5,9]

Aortic elastic properties are important predictors of cardiovascular morbidity and mortality. We did not find any independent relationship between OSA/AHI and thoracic aortic compliance. Hypertensive patients with OSA have the lowest aortic compliance compared with hypertensive patients without OSA or patients with OSA without hypertension. Thus, it seems that the principal determinant of aortic compliance in these patients is hypertension. Systolic blood pressure is known to hasten the fragmentation of fibrin, collagen deposition with secondary stiffening of the aortic wall. Although we did not find an independent effect of OSA on aortic compliance, the presence of hypertension and OSA result in lower aortic compliance compared with hypertensive patients without OSA, indicating that in hypertensive patients, the presence of OSA may have additional negative impact on the aortic compliance. Previous study has shown that increased sympathetic drive in OSA can accelerate the subclinical atherosclerotic process leading to additional impairment of aortic elasticity property in the setting of hypertension.[3] Besides, Narkiewicz et al demonstrated that hypertensive patients with OSA has underlying autonomic nervous system deregulation, characterized by reduced baroreflex sensitivity throughout the day conferring higher afterload on the vessel wall.[16]

To date, there is no specific treatment to attenuate dilatation of thoracic aorta in these patients besides antihypertensive medication and use of CPAP. We propose that early aggressive treatment of hypertension in OSA patients could potentially attenuate or reverse aortic dilatation.

Limitation

Our study has several limitations. The study population was predominantly male with AMI thus, the result of our study cannot be extrapolated to female patients as well as patients without AMI. In addition, the diagnosis of hypertension was based on the information given by the patients. All the subjects have underlying significant coronary artery disease and other comorbidities, so it is likely that their other comorbidities can affect the aortic distensibility. In addition, compared to studies using CT scan, echocardiographic measurement of the ascending aorta might not be as precise although we could not deny that transthoracic echocardiogram is a safe and easily available screening tool. Interobserver and intraobserver variabilities in the measurement of aortic diameter were not obtained in the present study. However, previous studies have demonstrated that aortic measurements using echocardiography has excellent reproducibility.

CONCLUSIONS

Hypertension is a common finding in male AMI patients with OSA. In these patients, increased afterload from systemic hypertension rather than mechanical stress on the aortic wall due to repeated episodes of apneas and hypopneas determines the thoracic aortic size and abnormalities in aortic functional indices. BMI and age are the other independent predictors of thoracic aortic dilatation.

ABBREVIATIONS

AHI, apnea-hypopnea index
AMI, acute myocardial infraction
BMI, body mass index
CPAP, continuous positive airway pressure
OSA, obstructive sleep apnea
R, correlation coefficient.

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DISCLOSURE STATEMENT

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REFERENCES

1. Sampol G, Romero O, Salas A, et al. Obstructive sleep apnea and thoracic aorta dissection. Am J Respir Crit Care Med 2003;168:1528-31.
2. Mitchell GF, Lacourciere Y, Ouellette JP, et al. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. Circulation 2003;108:1592-8.
3. Tsioufis C, Thomopoulos K, Dimitriadis K, et al. The incremental effect of obstructive sleep apnoea syndrome on arterial stiffness in newly diagnosed essential hypertensive subjects. J Hypertens 2007;25:141-6.
4. Vasan RS, Larson MG, Levy D. Determinants of echocardiographic aortic root size.The Framingham Heart Study. Circulation 1995;91:734-40.
5. Protogerou AD, Laaban JP, Czernichow S, et al. Structural and functional arterial properties in patients with obstructive sleep apnoea syndrome and cardiovascular comorbidities. J Hum Hypertens 2008;22:415-22.
6. Chi-Hang Lee, See-Meng Khoo, Eric Y Chong, et al. Obstructive sleep apnoea in patients admitted for acute myocardial infarction: prevalence, predictors, and effect on microvascular perfusion. Chest 2009;135:1488-95.
7. Peters J, Kindred MK, Robotham JL.Transient analysis of cardiopulmonary interactions. I. Diastolic events. J Appl Physiol 1988;64:1506-17.
8. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993;103:1763-8.
9. Serizawa N, Yumino D, Takagi A, et al. Obstructive sleep apnea is associated with greater thoracic aortic size. J Am Coll Cardiol 2008;52:885-6.
10. Cistulli PA, Wilcox I, Jeremy R, Sullivan CE. Aortic root dilatation in Marfan's syndrome: a contribution from obstructive sleep apnea? Chest 1997;111:1763-6.
11. Haentjens P, Van Meerhaeghe A, Moscariello A, et al. The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. Arch Intern Med 2007;167:757-64.
12. Norman D, Loredo JS, Nelesen RA, et al. Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. Hypertension 2006;47:840-5.
13. Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. Prog Cardiovasc Dis 2009;51:434-51.
14. Tsioufis C, Thomopoulos C, Stefanadis C. Obstructive sleep apnoea and hypertension: a growing clinical challenge. Hellenic J Cardiol 2008;49:299-302.
15. Das AM, Khayat R, Hypertension in obstructive sleep apnea: risk and therapy. Expert Rev Cardiovasc Ther 2009;7:619-26.
16. Narkiewicz K, Pesek CA, Kato M, Phillips BG, Davison DE, Somers VK. Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. Hypertension 1998;32:1039-43.