Effect of Obstructive Sleep Apnea on Cardiovascular Function in Obese Youth

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The increasing prevalence of overweight or obese children and adolescents is a significant global health concern. Although the effect of obesity on cardiovascular function has been investigated, little is known on the impact of associated obstructive sleep apnea (OSA) in obese youth. The aim of the present study was to investigate the influence of OSA on cardiovascular functional parameters in obese youth. This is a prospective single-center observational cross-sectional study. Forty-four obese patients and 44 age- and gender-matched control subjects were included. All patients underwent polysomnography and cardiovascular assessment including functional echocardiography and carotid-femoral pulse wave velocity (PWV). Obese patients had higher left ventricular (LV) mass/height$^{2.7}$, preserved LV systolic parameters, differences in LV diastolic parameters, and increased PWV and systolic blood pressure at rest compared with control group. In obese youth, 14 of 44 (32%) had OSA. There was no correlation between obesity and the apnea-hypopnea index (AHI). LV mass/height$^{2.7}$ significantly correlated with body mass index z-score ($r = 0.648$, $p < 0.001$) whereas PWV correlated with AHI ($r = 0.352$, $p = 0.038$). In obese patients, body mass index z-score was an independent predictor for LV mass/height$^{2.7}$ ($r = 0.61$, $p < 0.001$) and AHI was an independent predictor for higher PWV ($r = 0.352$, $p = 0.038$). In conclusion, both obesity and OSA influence cardiovascular performance in obese youth. Although obesity is associated with increased LV mass and reduced LV diastolic function, OSA is associated with changes in arterial stiffness. **(Am J Cardiol 2019;123:341−347)**

The increasing prevalence of overweight or obese children and adolescents is a significant global health challenge.[1−3] The downstream impact of childhood obesity on adult cardiovascular disease is a major public health concern.[4] In obese youth, early changes in vascular health as well as left ventricular (LV) structure and function have been observed.[5−7] Obstructive sleep apnea (OSA) is characterized by repetitive airway obstruction, intermittent hypoxia, periodic arousals, and sleep fragmentation. OSA can lead to cardiac adaptations in both left- and right-sided ventricular size and function.[8,14] There is a strong relation between obesity and OSA.[8] Studies showed up to 45% of obese adults and 60% of obese children are at risk for OSA.[9,10] However, the actual role of OSA in mediating cardiovascular risk in obese youth is not completely understood. The aim of the present study is to investigate cardiovascular changes in a group of obese youth with and without OSA and to investigate the independent influence of OSA on cardiovascular adaptation.

Methods

This is a single-center prospective observational cross-sectional study of obese children and adolescents patients from 8 to 18 years old who were referred to the sleep clinic with a history of snoring from 2012 to 2015. Obesity was defined as body mass index (BMI) greater than ninety-fifth centile for age and gender.[11] Patients were excluded from the study if they had known systemic hypertension, diabetes, dyslipidemia, Down syndrome, known underlying neuromuscular disorder, congenital heart disease, and diagnosed ventricular dysfunction or if they were unable to undergo or tolerate a polysomnography. All patients had an overnight polysomnography, an echocardiography for cardiac function assessment and carotid-femoral pulse wave velocity (PWV) analysis using Sphygmocor within a 3-month time frame. Informed consent and/or assent was obtained from both obese youth and their parents. The study protocol was approved by the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada. Echocardiographic and PWV results were compared with age- and gender-matched subjects selected from our healthy controls with no history of OSA or with BMI z-score > 2. Healthy volunteers consented to participate in research and underwent identical protocols for echocardiograms and PWV testing.

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https://doi.org/10.1016/j.amjcard.2018.09.038

Echocardiographic examinations were performed on a Vivid E9 ultrasound system (GE Ultrasound, Wauwatosa, WI, USA). Images were digitally stored and off-line analysis using EchoPAC software (version 201, GE). Image acquisitions and measurements were performed by the same experienced sonographer (CS) after published guidelines from the American Society of Echocardiography.[12] LV mass was calculated based on the Devereux formula.[13] LV mass index was calculated as LV mass in grams divided by height in meters to the 2.7th power.[14] The LV longitudinal strain was an average of 6 segments from apical 4 chamber view only and LV circumferential strain was an average of 18 segments obtained from the basal/mid/apical levels of LV from a parasternal short-axis window. Blood pressure and heart rate at rest for patients and healthy controls were obtained during the echo visit (an average of 3 blood pressure measurements at the end of the echo study by the same sonographer using standard procedures).

A pressure tonometer (Sphygmocor, AtCor, Itasca, Illinois) was used to transcutaneous record the pressure pulse waveforms in the carotid and femoral arteries. The difference between time to onset of carotid pulse and time to onset of femoral pulse was calculated as PWV time interval. PWV distance was defined as the difference between the proximal distance (from suprasternal notch to carotid artery site) and distal distance (from suprasternal notch to femoral artery site). PWV was calculated as the PWV distance divided by PWV time interval. At least 2 PWVs were measured. The test was repeated if the 2 measurements had $>10\%$ difference. The average of the 2 results with $<10\%$ difference was used for further analysis.

Polysomnography was undertaken according to the American Academy of Sleep Medicine international guidelines using Natus Sleepworks system (Natus Medical Inc., Pleasanton, California).[15] Polysomnography measurements included electroencephalogram, electro-oculogram, submental electromyogram, chest wall, and abdominal movements. Other respiratory measurements included nasal air flow, oxygen saturations using a Massimo pulse oximeter (Irvine, California), transcutaneous carbon dioxide levels using a Sentec carbon dioxide sensor (Therwil, Switzerland) and end-tidal carbon dioxide levels using a BCI Capnocheck unit. All respiratory events were scored according to the American Academy of Sleep Medicine scoring guidelines by a registered certified polysomnographic technician who was blinded to the clinical status of the patients.[15] All the sleep studies were reviewed and interpreted by experienced pediatric sleep physicians. An obstructive apnea event was scored when airflow dropped at least 90% from baseline with chest and/or abdominal motion throughout the entire event for a minimum of 2 baseline breaths. A hypopnea event was scored when airflow dropped at least 50% from baseline, for a minimum of 2 baseline breaths. The hypopnea event must have been accompanied by either (1) a minimum 3% decrease in oxygen desaturation, (2) an arousal, or (3) an awakening. OSA was diagnosed according to the obstructive apnea-hypopnea index (AHI) defined as the number of obstructive apneas, hypopneas, and mixed apneas per hour during sleep. OSA was diagnosed if the obstructive AHI was >5 events per hour.

SPSS 20 (IBM) was used for analysis. Continuous data were expressed as mean ± standard deviation, except some skewed polysomnography variables were expressed as median and range. AHI, arousal index, and desaturation index from polysomnography were $\log_{10}$ transformed to improve normality, which were used in the correlation and regression analyses. Z-scores for BMI[11] and systolic and diastolic blood pressures at rest[16] were generated using the corresponding sources and were used for all analyses. The difference of the mean between 2 independent groups was compared using independent samples *t* test or Mann-Whitney test. Chi-square and Fisher's exact tests were used to test the association between 2 categorical variables. Pearson correlation was applied to test the correlations between 2 continuous variables. Multivariable regression analysis (stepwise method) was used to predict (1) LV hypertrophy from age, gender, BMI, AHI, desaturation index, total arousal index, systolic and diastolic blood pressure; (2) PWV from age, gender, BMI, height, AHI, blood pressure, and heart rate. A p value of <0.05 was considered statistically significant.

Results

Forty-four obese youth were included. The mean (range) age was 14 ± 3 (9 to 18) years, and mean height was 162 ± 11 cm. The mean weight and BMI were 95 ± 28 kg and 37 ± 10 kg/m^2, respectively. The characteristics and cardiovascular performance of the entire obese patient group and gender-matched controls are summarized in Table 1. Systolic blood pressure at rest was significantly higher in the obese group compared with the controls, although none of the patients were diagnosed with hypertension clinically. Based on published criteria defining LV hypertrophy,[17] 14 of 44 (32%) patients had LV hypertrophy (8 men with LV mass/height$^{2.7}$ >45 g/m$^{2.7}$ and 6 women with LV mass/height$^{2.7}$ >40 g/m$^{2.7}$. The obese patients had larger cardiac dimensions, higher LV mass, and altered LV diastolic function. There was no difference in PWV between obese patients and controls.

The median (range) AHI was 2.35 (0 to 67);14 (32%) patients had AHI >5 and 10 (23%) patients had AHI from 1.5 to 5.0. Polysomnogram data are shown in Table 2. Overall, patients with OSA had significantly higher arousal index and desaturation index. There were no significant differences in general characteristics or cardiac performance between the OSA and no-OSA groups (Table 3). Patients with OSA had significantly higher PWV ($p=0.009$; Figure 1).

Within the obese patients, there was a significant correlation between BMI and LV hypertrophy ($r=0.648$, $p<0.001$; Figure 2) and a weak but significant correlation between BMI and LV E/E' ratio ($r=0.369$, $p=0.015$). There were no correlations between BMI, LV systolic functional parameters, or PWV. AHI did not correlate with LV hypertrophy, LV systolic and diastolic parameters. There was a weak but significant correlation between AHI and PWV ($r=0.352$, $p=0.038$). Desaturation index was correlated with PWV ($r=0.394$, $p=0.025$). No correlation was observed between BMI and AHI or LV hypertrophy and PWV (Table 4).

Table 1
Anthropometrics and cardiovascular function of obese youth and healthy controls

Variables	Obesity (n = 44)	Controls (n = 44)	p
Age (years)	13.7 ± 2.9	13.6 ± 2.9	NS
Gender, male (%)	21 (48%)	21 (48%)	NS
Height (cm)	162 ± 11	162 ± 14	NS
Weight (kg)	95 ± 28	52 ± 15	< 0.001
Body mass index (kg/m^2)	36 ± 8.6	20 ± 3.3	< 0.001
Body mass index, z-score	2.4 ± 0.41	−0.035 ± 1.2	< 0.001
Heart rate (beats per minute)	74 ± 14	66 ± 12	0.003
Systolic blood pressure, z-score	0.62 ± 1.2	−0.052 ± 0.8	0.002
Diastolic blood pressure, z-score	−0.47 ± 0.63	−0.055 ± 0.63	NS
Interventricular septum thickness (mm)	8.2 ± 1.5	7.2 ± 1.1	< 0.001
Left ventricular posterior wall thickness (mm)	7.5 ± 1.4	6.3 ± 1.1	< 0.001
Left ventricular mass (g)	139 ± 43	98 ± 26	< 0.001
Left ventricular mass index by body surface area (g/m^2)	70 ± 14	64 ± 12	0.03
Left ventricular mass index by height$^{2.7}$ (g/m$^{2.7}$)	38 ± 9.2	27 ± 6.2	< 0.001
Left atrial dimension (cm)	3.5 ± 0.41	2.9 ± 0.33	< 0.001
Left ventricular end-diastolic dimension (cm)	5.1 ± 0.46	4.6 ± 0.46	< 0.001
Left ventricular fractional shortening (%)	38 ± 3.7	38 ± 4.1	NS
Mitral valve Doppler early diastolic wave velocity (cm/s)	106 ± 16.6	100 ± 16.7	0.02
Mitral valve Doppler late diastolic wave velocity (cm/s)	51 ± 13	43 ± 12	< 0.001
Mitral valve Doppler early/late diastolic wave velocity ratio	2.2 ± 0.58	2.4 ± 0.75	NS
Mitral valve Doppler early diastolic wave deceleration time (ms)	161 ± 25	150 ± 19	0.03
Left ventricular isovolumic relaxation time (ms)	73 ± 8.5	73 ± 7.6	NS
Tissue Doppler left ventricular lateral systolic velocity (cm/s)	10 ± 1.9	12 ± 2.0	0.009
Tissue Doppler left ventricular lateral early diastolic velocity (cm/s)	18 ± 2.8	19 ± 2.7	0.03
Mitral valve Doppler early diastolic wave velocity/tissue Doppler left ventricular lateral early diastolic velocity	6.2 ± 1.4	5.3 ± 1.1	0.002
Left ventricular circumferential stain (%)	21 ± 1.8	20 ± 1.5	< 0.001
Left ventricular longitudinal strain (%)	20 ± 2.2	20 ± 1.6	NS
Pulse wave velocity carotid-femoral (m/s)	5.5 ± 0.96	5.1 ± 0.98	NS

NS: p ≥ 0.05.

For predicting LV hypertrophy, age, gender, BMI, AHI, and blood pressure were included in the model. Multivariate linear regression analysis (stepwise method) showed that BMI was the only significant predictor ($p < 0.001$). The model with BMI significantly predicted 37% of the change in LV hypertrophy. For PWV, age, gender, BMI, AHI, blood pressure, height, and heart rate were included in the model. Multivariate linear regression analysis (stepwise method) showed that AHI was the only significant predictor ($p = 0.038$) of PWV.

Table 2
Polysomnography results in obese youth with and without obstructive sleep apnea

	Obstructive sleep apnea		
Variables	Yes (n = 14)	No (n = 30)	p
Apnea-hypopnea index (per hour)	20 (5.1−67)	0.95 (0−4.8)	< 0.001
Total sleep time (minute)	348 ± 55	362 ± 54	NS
Sleep efficiency (%)	79 ± 10	84 ± 9.7	NS
Wake after sleep onset (minute)	44 (11−109)	31 (1.5−160)	0.06
Stage 1 duration (%)	11 ± 6.1	5.9 ± 3.7	0.003
Stage 2 duration (%)	49 ± 6.3	52 ± 7.7	NS
Stage 3 duration (%)	24 ± 7.5	25 ± 8.1	NS
Rapid eye movement sleep duration (%)	16 ± 5.6	16 ± 6.5	NS
Total arousal index (per hour)	18 (7.5−40)	7.5 (3.9−28)	< 0.001
Desaturation index (mean) desaturations (per hour)	1.3 (0−50)	0.5 (0−5.7)	< 0.001
Mean peripheral capillary oxygen saturation for total sleep time (%)	97 ± 0.75	98 ± 1	0.06
Minimum peripheral capillary oxygen saturation for total sleep time (%)	85 ± 7.9	89 ± 8.6	NS
Percentage of time when peripheral capillary oxygen saturation < 90% (%)	0.1 (0−4.4)	0 (0−1.4)	0.04
Peak end-tidal carbon dioxide (mm Hg)	50 ± 4.1	49 ± 3.2	NS
Mean end-tidal carbon dioxide (mm Hg)	44 ± 3.4	43 ± 2.7	NS
Percentage of time with end-tidal carbon dioxide > 50 mm Hg (%)	0.4 (0−15)	0 (0−6.3)	0.09

NS: p ≥ 0.05.

Table 3
Anthropometrics and cardiovascular function of obese youth with and without obstructive sleep apnea (apnea-hypopnea index ≤5 vs apnea-hypopnea index >5)

	Obstructive sleep apnea		
Variables	Yes (n = 14)	No (n = 30)	p
Age (years)	14 ± 3.3	14 ± 2.7	NS
Gender, male (%)	10 (71)	11 (37)	0.052
Height (cm)	160 ± 11	162 ± 11	NS
Weight (kg)	95 ± 31	95 ± 27	NS
Body mass index (kg/m^2)	36 ± 9.5	37 ± 11	NS
Body mass index, z-score	2.5 ± 0.48	2.4 ± 0.38	NS
Heart Rate (beats per minute)	79 ± 16	72 ± 12	NS
Systolic blood pressure, z-score	0.62 ± 1.6	0.62 ± 1	NS
Diastolic blood pressure, z-score	−0.46 ± 0.77	−0.48 ± 0.57	NS
Interventricular septum thickness (mm)	8.8 ± 1.5	7.9 ± 1.5	NS
Left ventricular posterior wall thickness (mm)	7.7 ± 1.5	7.4 ± 1.3	NS
Left ventricular mass (g)	148 ± 46	135 ± 42	NS
Left ventricular mass index by body surface area (g/m^2)	74 ± 13	68 ± 14	NS
Left ventricular mass index by height$^{2.7}$ (g/m$^{2.7}$)	41 ± 8.6	38 ± 9.2	NS
Left atrial dimension (cm)	3.5 ± 0.53	3.5 ± 0.36	NS
Left ventricular end-diastolic dimension (cm)	5.1 ± 0.52	5.1 ± 0.43	NS
Left ventricular fractional shortening (%)	39 ± 3.5	38 ± 3.8	NS
Mitral valve Doppler early diastolic wave velocity (cm/s)	105 ± 16	106 ± 17	NS
Mitral valve Doppler late diastolic wave velocity (cm/s)	53 ± 13	51 ± 14	NS
Mitral valve Doppler early/late diastolic wave velocity ratio	2.1 ± 0.55	2.2 ± 0.6	NS
Mitral valve Doppler early diastolic wave deceleration time (msec)	158 ± 11	162 ± 29	NS
Left ventricular isovolumic relaxation time (msec)	76 ± 9.8	72 ± 8	NS
Tissue Doppler left ventricular lateral systolic velocity (cm/s)	11 ± 1.7	10 ± 2	NS
Tissue Doppler left ventricular lateral early diastolic velocity (cm/s)	17 ± 2.7	18 ± 2.9	NS
Mitral valve Doppler early diastolic wave velocity/tissue Doppler left ventricular lateral early diastolic velocity	6.3 ± 1.3	6.1 ± 1.4	NS
Left ventricular circumferential stain (%)	21 ± 1.8	22 ± 1.7	NS
Left ventricular longitudinal strain (%)	20 ± 2.1	21 ± 2.3	NS
Pulse wave velocity carotid-femoral (m/s)	6 ± 1.1	5.2 ± 0.74	0.009

NS: p ≥0.05.

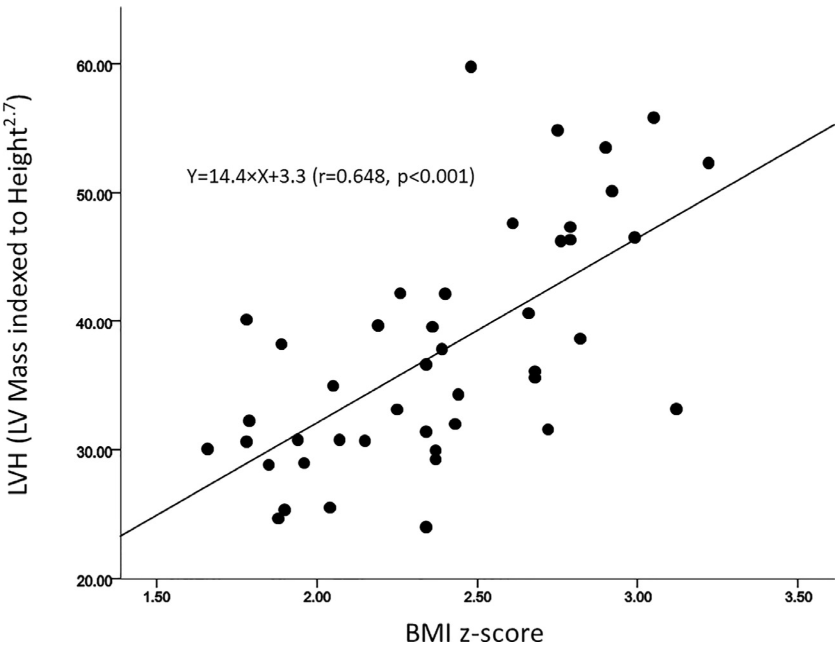

Figure 1. Association between BMI z-score and LV hypertrophy expressed by LV mass indexed to height$^{2.7}$. The figure includes a scatterplot and a regression line. The "X" represents BMI z-score, "Y" represents LV mass indexed to hieght$^{2.7}$. The result is from bivariate linear regression analysis. BMI = body mass index; LV = left ventricle; LV hypertrophy = left ventricular hypertrophy.

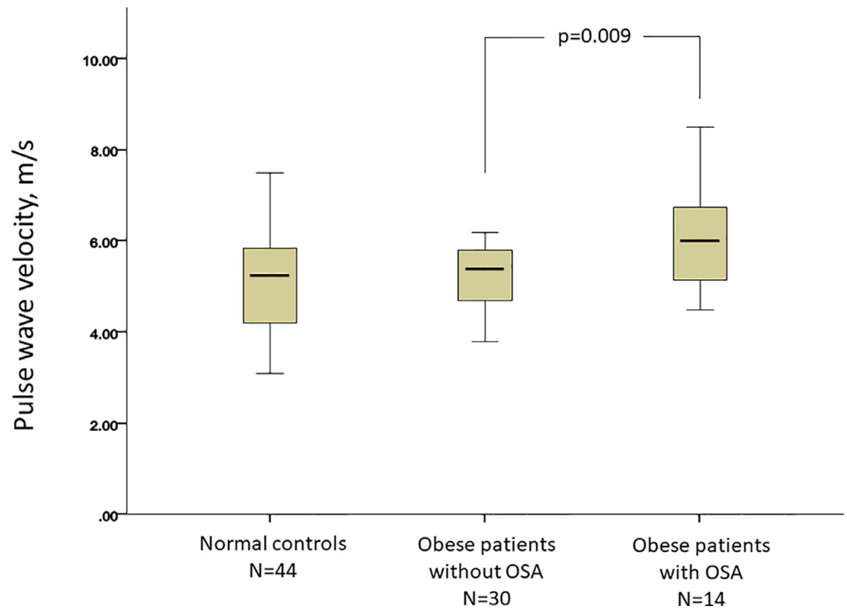

Figure 2. Comparing the pulse wave velocities in normal controls, obese youth with and without OSA. Boxplot is used to describe the data distribution in each subgroup. There is a significant difference between patients with and without OSA. OSA = obstructive sleep apnea.

Discussion

The present study confirms that obese youth have increased LV mass and mild differences in LV diastolic functional parameters. Changes in LV mass were mainly determined by BMI and not OSA. Vascular stiffness in patients with obesity was higher than in controls and within the obesity group, OSA, rather than BMI, was an independent predictor of vascular stiffness.

Quantifying LV wall thickness in obese patients is challenging as LV mass should be normalized for body size as this influences heart size independent of pathologic remodeling. In adult cardiology, the most generally accepted method corrects LV mass for height to the 2.7th power.[14] This method however may not work well in children as Khoury et al showed that the index varied with age, suggesting that LV mass/height$^{2.7}$ must be corrected for age, particularly in children <9 years and shorter than 140 cm.[17,18] As most patients in our study were older than 9 years and >140 cm, the use of LV mass/height$^{2.7}$ seems appropriate. In the present study, we observed that obese youth have significantly increased LV mass. Multiple physiologic pathways, including hemodynamic factors and non-hemodynamic factors, have been hypothesized linking obesity with increased LV mass.[19] Obese patients can have associated OSA which can lead to LV hypertrophy through sympathetic nervous system activation and associated catecholamine release.[20] In present study, we demonstrated that BMI was the primary predictor for LV hypertrophy. We could not observe an association between AHI or any of the other polysomnography variables and LV hypertrophy. This contrasts with the findings of Amin et al who found that AHI was predictive of LV hypertrophy.[21] The differences in findings between the 2 studies could be due to lower BMI and higher frequency of OSA in Amin's study compared with our study (mean BMI 24kg/m^2 with 32% with AHI > 10 vs 36 Kg/m^2 with 27% with AHI > 10, respectively).

LV systolic and diastolic dysfunction has been reported in adult obese patients, which is related to both severity and duration of excess adiposity.[7] The early signs of LV dysfunction can be observed in childhood.[19] Our data showed obese patients had a slightly but statistically significant higher LV circumferential strain, with no change in other systolic parameters suggesting LV systolic function is preserved. In contrast, our patients demonstrated small but significant differences in diastolic parameters with a longer mitral valve E deceleration time, lower tissue Doppler E' velocity ratio, and elevated LV E/E' ratio. This seems to indicate a mild reduction in early LV relaxation possibly related to the observed LV hypertrophy. These early changes in diastolic function require further follow-up as they may indicate pathologic remodeling and adaptation.

Table 4
Associations among body mass index/apnea-hypopnea index /left ventricular hypertrophy/pulse wave velocity in obese youth

	Body mass index	Apnea-hypopnea index	Left ventricular hypertrophy*	Pulse wave velocity
Body mass Index		NS	r = 0.648, p < 0.001	NS
Apnea-hypopnea index	NS		NS	r = 0.352, p = 0.038
Left ventricular hypertrophy*	r = 0.648, p < 0.001	NS		NS
Pulse wave velocity	NS	r = 0.352, p = 0.038	NS	

* Represented by LV mass index by height$^{2.7}$. NS: $p \geq 0.05$.

Our study observed higher central PWVs in OSA patients compared with non-OSA patients reflecting increased arterial stiffness associated with OSA. Although the independent role of OSA and its impact on PWV in adults has been reported,[22] to our knowledge, this is the first study to show the impact of OSA on PWV in obese children, rather than BMI and blood pressure. The association between OSA and PWV is of clinical significance as increased arterial stiffness impacts LV afterload and could lead to development of LV hypertrophy and adverse LV remodeling.[23] As this is a pediatric cohort who does not have longstanding OSA, it likely explains the lack of an association between OSA and LV hypertrophy or other cardiac functional indexes.

The lack of association between PWV and BMI in this study requires further consideration. In 1 study involving 102 children and adolescents, both obesity and hypertension were significant predictors of PWV.[24] Further, Caterini et al also showed that magnetic resonance imaging derived PWV was associated with obesity.[25] However, in both studies, polysomnography was not performed and thus the presence and contribution of OSA is unknown. Lower PWV in young obese patients especially during puberty was described as an interesting phenomenon coined a "paradoxical decrease."[26] Although difficult to explain, it is believed that obesity may not predict PWV at this age as there is short-term adaptation in obese adolescents during which PWV is actually low before it increases.[26]

The limitations of this study require some consideration. We did not use z-scores for PWV. Compared with other variables, the sources available for PWV percentiles are relatively rare. Reusz et al[27] published reference tables involving a cohort of 1,000 children and teenagers. However, the data are from a non-North American population, which may not be suitable as a reference for our patients. The major determinants of PWV were age, height, blood pressure, and heart rate.[27–29] and these factors were included in our multiple regression analyses. Our sample size of patients with OSA was rather small and larger datasets of obese youth with OSA are needed to verify these findings as well as to further explore the relation between OSA and left ventricular hypertrophy as well as BMI and PWV. Finally, our findings are limited to obese youth with moderate to severe OSA. These results might not be applicable for obese children and adolescents with other various comorbidities.[30]

Obese youth with co-existing OSA are at an increased risk for cardiovascular disease. In obese youth, the presence of OSA is associated with increased arterial stiffness and obesity was associated with an increased LV mass, and a mild reduction of LV diastolic function. Our results suggest the necessity of screening for OSA in all obese subjects. Targeted therapeutic interventions for both obesity and OSA are needed to reduce cardiovascular risk in this vulnerable population. Although reducing obesity may benefit reducing LV hypertrophy, treating OSA could lead to decreased arterial stiffness.

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