Interrelationships between obesity, obstructive sleep apnea syndrome and cardiovascular risk in obese adolescents

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Abstract

Background/Objectives—Obstructive sleep apnea syndrome (OSAS) may be a cardiovascular disease (CVD) risk factor independently of obesity in adults. Pediatric studies have associated OSAS with endothelial dysfunction, but few studies have examined relationships between OSAS and macrovascular sequelae. Our objective was to examine OSAS's independent contribution to macrovascular CVD risk measures in obese adolescents.

Subjects/Methods—This cross-sectional observational study was conducted at Children's Hospital of Philadelphia Clinical Research and Academic Sleep Centers, and University of Pennsylvania Vascular Research Unit. 31 obese non-diabetic adolescents underwent

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anthropometric measurements, overnight polysomnography, fasting laboratory draw, and cardiovascular imaging. Cardiovascular outcome measures included maximal carotid intima-media thickness (cIMTmax), a measure of carotid structural changes, and carotid-femoral pulse wave velocity (CFPWV), an aortic stiffness measure whose relationship vis-à-vis OSAS in children has not been previously examined. Carotid diameter and augmentation index (AIx, measuring central pressure augmentation from wave reflections) were assessed. Potential confounding variables examined included blood pressure, lipoproteins, high-sensitivity C-reactive protein, insulin and glucose.

Results—The apnea hypopnea index, a primary OSAS measure, was not associated with cIMTmax, carotid diameter, CFPWV or AIx. BMI associated positively with cIMTmax (r=0.52, p=0.006) and CFPWV (r=0.45, p=0.01). Mean asleep end-tidal CO_2 was negatively associated with carotid diameter (r=−0.63, p<0.0005). Insulin levels were negatively associated with AIx (r= −0.53, p=0.02).

Conclusions—OSAS did not predict carotid structural changes or arterial stiffness independently of BMI in obese adolescents. Higher insulin levels associated with lower central pressure wave augmentation. Finally, long-term hypercapnia may predispose to carotid narrowing.

Key terms

Arterial stiffness; atherosclerosis; sleep apnea; obesity; cardiovascular risk; adolescents

Introduction

The prevalence of pediatric obesity has increased in recent decades; 16.9% of U.S. children and adolescents are now obese(1). This trend has been accompanied by an increased prevalence of associated co-morbidities, including type 2 diabetes mellitus (T2DM)(2), the metabolic syndrome (a cluster of cardiovascular risk factors consisting of central obesity, insulin resistance, hypertension, and dyslipidemia)(3) and other measures of cardiovascular risk(4). The increased prevalence of cardiovascular risk factors in children and adolescents is a worrisome trend, suggesting the possibility of widespread onset of overt cardiovascular disease (CVD) decades younger than in the past(5). While weight loss reduces the risk of developing obesity-related co-morbidities(6), many find long-term weight loss maintenance difficult(7). Thus, it is imperative to identify other potentially modifiable CVD risk factors in the pediatric population.

Obstructive sleep apnea syndrome (OSAS), a common co-morbidity of obesity(8), is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns(9), leading to sleep fragmentation and decreased oxyhemoglobin saturation(10). In adults, OSAS may increase risk for T2DM(11), atherosclerosis(12), vascular stiffening(13) (another risk factor for CVD), and incident CVD(14) independently of obesity. Pediatric data about the metabolic effects of OSAS are limited; however, OSAS has been associated with increased risk of the metabolic syndrome and insulin resistance in children(15). Few studies have specifically examined the link between CVD risk factors and OSAS in children: one such study showed increased sympathetic vascular reactivity in

children with OSAS(16). Another study found that OSAS in normal-weight children was associated with blunted vascular endothelial response, which resolved (in a subset) following adenotonsillectomy(17). We hypothesized that, in obese adolescents, OSAS posed an independent risk factor for macrovascular CVD risk markers, namely carotid structural changes and large artery stiffness, independently of 1) degree of obesity and 2) other potential predictors of CVD risk such as hypertension, dyslipidemia, inflammation, insulin resistance, and anthropometric surrogate measures of visceral adiposity.

Methods

This was an observational, cross-sectional study of obese adolescents, examining the association between OSAS (primary measure: the apnea hypopnea index, or AHI) and several macrovascular measures of structure and function associated with CVD risk: (1) carotid structural change: primary outcome measure: carotid intima-media thickness and (2) arterial stiffness - primary measure: carotid-femoral pulse wave velocity. Other imaging measures of macrovascular structure and function assessed included common carotid artery (CCA) diameter and the augmentation index (AIx, calculated as the ratio of the augmentation pressure to pulse pressure, or AP/PP) an index of central pressure augmentation from wave reflections. The impact of other established CVD risk measures – blood pressure, homeostasis model assessment of insulin resistance (HOMA-IR), lipoprotein profiles including apolipoprotein B (ApoB), and inflammation as measured by high-sensitivity CRP (hsCRP) – and the impact of central adiposity (assessed by the surrogate anthropometric measurements of waist circumference and sagittal abdominal diameter) upon the macrovascular CVD risk outcomes of interest were also examined. Investigators interpreting the various studies were blinded to metabolic status of the participants.

This study was approved by the Children's Hospital of Philadelphia (CHOP) Institutional Review Board. Written informed consent and age-appropriate assent were obtained from all parents or guardians and participants before enrollment.

Study Participants

Participants were recruited from the CHOP endocrinology clinic and from the general population via advertisements. Inclusion criteria included obesity (BMI 95th percentile for age and sex), pubertal status (Tanner stages 2–5), and ages 12–17 years. Exclusion criteria included known type 1 or type 2 diabetes, known OSAS requiring treatment, CVD history, pregnancy, presence of major organ system illness or genetic syndrome, treatment with medications known to affect sleep, insulin sensitivity or lipid profiles, and significant smoking history (>1/2 pack per day).

Study Protocol

Tanner staging for puberty was based on breast development in girls and testicular size in boys. Weight was measured using a calibrated digital scale (Scaletronix, White Plains, NY). Height was measured using a wall-mounted stadiometer (Holtain Inc., Crymych, UK). Body Mass Index (BMI) percentiles were assessed using age- and gender-specific reference data(18). Urine pregnancy tests were performed for all females. Brachial blood pressure

(BP) was recorded in triplicate using an automatic oscillometric device (Dinamap, Critikon Inc, Tampa, FL) using appropriately sized cuffs; results were averaged. Anthropometric measures were obtained in triplicate. Waist circumference (to 0.1 cm) was measured in triplicate at the level of the umbilicus. Sagittal abdominal diameter was measured with participant supine and knees flexed, as the vertical distance at end-expiration between abdominal caliper blades (Seritex Inc., East Rutherford NJ) placed below and above the trunk slightly proximal to the iliac crest. Neck circumference was measured at the level of the thyroid cartilage. Percentiles and Z-scores were calculated for all systolic and diastolic BP (SBP and DBP) readings(19). Study procedures included fasting blood drawn for biochemical analyses, hemodynamic testing, vascular imaging studies, and overnight polysomnography, as described below.

Biochemical measurements

Fasting lipid profile was performed using an enzymatic colorimetric assay (Roche Diagnostics), and ApoB, the core particle of low- and very low-density lipoproteins, was isolated via an immunoturbidimetric assay (Roche Diagnostics; 20–400 mg/dL); both were run on a Roche-Hitachi 912 analyzer (Uster, Switzerland). Low-density lipoprotein (LDL) cholesterol was calculated using the Freidewald equation(20). HsCRP was measured via particle-enhanced immunonephelometry via the BN^{TM} II System (Siemens CardioPhase®, Tarrytown, NY; 0.15–9.50 mg/L). Whole blood glucose was measured by the glucose oxidase method (Sensolite Nova glucose meter). Fasting plasma insulin was measured by radioimmunoassay (LINCO, St. Charles Mo). Homeostasis model assessment of insulin resistance (HOMA-IR), a validated insulin sensitivity measure(21), was calculated as [Fasting insulin (microIU/mL) * Fasting glucose (mmol/L)]/22.5.

Imaging Studies and hemodynamic measurements

A. Carotid structural changes - carotid intima-media thickness (IMT)—Carotid IMT measures remodeling of the intimal and medial layers of the carotid artery wall and may represent a risk factor for atherosclerosis. Bilateral B-mode carotid artery images (Siemens Acuson Sequoia ultrasound system, Mountain View, CA) were acquired using a linear array 9L4 transducer. Distal common carotid artery (CCA) posterior wall was measured one centimeter below the bifurcation. Ten sequential still frames coinciding with the electrocardiogram (ECG) R wave were recorded. IMT was measured (Carotid Analyzer edge-detection program, Medical Imaging Applications, Coralville, Iowa) as the distance between echoes arising from the blood-intima and media-adventitia interfaces(22); maximal CCA IMT (cIMTmax) was analyzed. CCA diameter was measured as the distance between the two blood-intima interfaces. The far wall was used for this study because measurement of near-wall thickness is more subject to artifacts of ultrasound imaging(23). Right and left cIMTmax and CCA diameter values were averaged, and the resultant means were used for analyses. CIMTmax rather than mean cIMTmax was used because cIMTmax is a better predictor of end-organ damage and CVD risk(24).

B. Arterial stiffness - Carotid-femoral pulse wave velocity (CFPWV)—Large artery stiffening as assessed by CFPWV is a manifestation of vascular aging that is exacerbated by conditions such as diabetes mellitus(25) and independently predicts

cardiovascular events and mortality, especially in younger adults(26). CFPWV is defined as the distance the pulse wave must travel divided by the time required for pulse wave propagation from the carotid (a surrogate for the proximal aorta) to the femoral arteries. Higher values indicate greater arterial stiffness. CFPWV was assessed in triplicate (results averaged) using the applanation tonometry principle (Millar tonometer, Millar Instruments; Houston, TX), using a commercially available system (SphygmoCor Vx System, AtCor Medical; Sydney, Australia) which includes acquisition software for non-invasive arterial pulse recording. The tonometer was used to record carotid and femoral artery waveforms in the supine position. Time delay between the carotid and femoral sites was estimated using the ECG R wave as a fiducial point. CFPWV was calculated as distance/ time(27).

Augmentation Index AP/PP (AIx): The AIx measures the relative amount of central pressure augmentation from wave reflection. The augmentation pressure (AP) is the difference between the central pressure waveform's second and first systolic peaks (P2-P1). The AIx is defined as the ratio of AP to pulse pressure (PP) (AIx = AP/PP). Higher values indicate greater pressure augmentation. AIx was calculated from the BP waveform assessed by applanation tonometry as described above.

CFPWV and AIx measurements were performed by a single investigator (DK).

Overnight polysomnography

Polysomnographic data were recorded using a Rembrandt polysomnography system (Embla, Broomfield, CO). Recorded parameters included the following: electroencephalography (F4/M1, C4/M1, O2/M1, F3/M2, C3/M2, O3/M2); left and right electrooculogram; submental electromyogram; bilateral tibial electromyograms; oronasal airflow with 3-pronged thermistor (Pro-Tech Services, Inc., Mukilteo, WA); nasal pressure (Pro-Tech Services, Inc., Mukilteo, WA); rib cage and abdominal wall motion via respiratory impedance plethysmography (Viasys Healthcare, Yorba Linda, CA); arterial oxygen saturation (SpO_2) with pulse waveform; end-tidal PCO_2 (E_TCO_2), measured at the nose via infrared capnometry (Novametrix Medical Systems, Inc., Wallingford, CT); and electrocardiogram. Sleep architecture and respiratory parameters (including the AHI, arousal index, lowest and mean SpO_2, and peak and mean E_TCO_2) were scored using standard pediatric criteria; apneas were defined as >90% decrement in airflow lasting for a minimum of 2 breaths, and hypopneas were defined as >50% decrement in airflow lasting a minimum of 2 breaths and accompanied by 3% oxyhemoglobin desaturation and/or EEG arousal(28). The AHI cutoff utilized to define OSAS was 1.5 events/hour(29, 30). Hypoventilation was defined as E_TCO_2>50 torr for >25% of total sleep time(28). Secondary OSAS measures were also examined in relationship to cardiovascular imaging measures, including mean SpO2 in REM and NREM sleep, obstructive apneas, obstructive hypopneas, mixed apneas, mixed hypopneas, central apneas, central hypopneas, and minimal and maximal heart rate while asleep. Polysomnograms were scored by sleep technologists and read by a board certified sleep physician (CLM), all of whom were blinded to the subjects' metabolic and cardiovascular results.

Statistical analysis

Statistical analysis was performed using SPSS Statistics v18 analysis software (Chicago, IL). A p-value 0.05 was considered statistically significant. Non-normally distributed data was transformed (e.g. natural logarithmic transformation) prior to statistical analyses to normalize the distribution. Pearson or Spearman correlation coefficients were used to examine associations between OSAS measures (AHI, arousal index, lowest and mean SpO_2, and peak and mean E_TCO_2) and CVD risk markers (primarily imaging measures - cIMTmax, carotid artery diameter, cfPWV, AIx, and other secondary measures, such as heart rate, blood pressure, and biochemical parameters such as hsCRP, apolipoprotein B, fasting lipid profile, and HOMA-IR). A sample size of 30 participants provided 80% power to detect a correlation of 0.49 or greater between AHI (the primary OSAS measure examined) and carotid IMT, the cardiovascular risk measure on which the study was powered; sample size calculations were based upon the study by Saletu *et al.* that reported a correlation between carotid IMT and AHI of 0.6 in adults(31). Student's T-test or Mann-Whitney U tests were used to compare values of continuous variables between sexes. As few participants were in Tanner 2 or 3 pubertal stages, those participants were combined into a larger group (Tanner 2/3) for analysis purposes. ANOVA or Kruskal-Wallis tests were utilized to compare mean values of continuous variables between pubertal stages. Linear regression models evaluated the relationship between obesity and CVD risk factors while controlling for OSAS primarily (after inclusion of BMI in the model) and secondarily for other potential confounding variables, e.g. age, sex, Tanner stage, and/or mean arterial pressure (MAP) or heart rate (HR). For a multiple linear regression model which included 4 covariates with an R^2 of 0.20, a sample size of 30 provided 80% power to detect, at the 0.05 significance level, an R^2 increase of 0.18 or greater due to inclusion of AHI in the regression model. Given the primary hypothesis that OSAS contributes to CVD risk independently of obesity, BMI was entered at the first step of the regression model, and AHI (natural-log transformed due to non-normal distribution) was entered at the second step. In a third step, covariates which had potential physiologic significance or confounding (e.g. HR and MAP for CFPWV and for AIx), showed significant mean differences between groups (sex, Tanner staging), or which associated significantly with the outcome variable in question on bivariate correlation analyses were included in a stepwise model serially so as to avoid over-fitting by not exceeding 4 variables in any given regression model. Variables included serially in all models at the stepwise regression stage included age (which can impact all above variables), waist circumference and sagittal abdominal diameter (to evaluate whether central obesity was a predominant contributor over generalized obesity), and HOMA-IR. Any significant predictor of the outcome variable (e.g. age, sex) was kept in the final model while other variables were serially tested.

Results

Study Participants

Thirty-one adolescents were studied. Descriptive characteristics of study participants are presented in Table 1. All but four subjects were African-American and only three subjects were Hispanic; thus, data could not be meaningfully analyzed by race and ethnicity. Polysomnography results and cardiovascular risk measure results in table 2. As only four

subjects did not meet pediatric criteria for OSAS (AHI<1.5), differences in cardiovascular parameters between subjects with and without OSAS could not be assessed. No participant was pregnant. Only 16% had HDL<35 and only 3% had triglycerides>150 mg/dL; only two participants had SBPs above the 95th percentile. One participant's CFPWV, of 7.5 m/sec, was over 5 standard deviations higher than the mean CFPWV value of all other participants (ranging from 4.1–5.9 m/sec); he was excluded from PWV analyses as an outlier. Males had significantly greater mean CCA diameters than females (6.7±0.4 vs. 6.3±0.5 mm, p=0.02). CIMTmax, CFPWV and AIx values did not differ significantly between males and females (data not shown). Sleep and biochemical parameters did not differ significantly between male and female participants (data not shown). No primary CVD or OSAS risk measure differed significantly among pubertal stages. Of the secondary cardiovascular risk measures examined, only fasting insulin and HOMA-IR differed significantly among pubertal stages, being considerably higher in the mid-pubertal groups than in the end-pubertal group: insulin values were 31.9, 32.5, and 19.1 microIU/mL for Tanner stages 2/3, 4, and 5 respectively, p-value=0.04, and HOMA-IR values were 7.20, 7.27 and 4.27 for Tanner stages 2/3, 4, and 5 respectively, p-value=0.03.

A. PREDICTORS OF CAROTID IMT AND DIAMETER—No significant associations were seen between any measure of OSAS and cIMTmax (table 3). However, a strong negative association was uncovered between CCA diameter and mean E_TCO_2 (table 3 and figure 1). Participants displayed a range of E_TCO_2 values (table 2), with 26% having E_TCO_2>50 torr for >10% of total sleep time, but only two participants met clinical criteria for hypoventilation(28), so the potential contribution of hypoventilation could not be assessed further.

We also examined the relationships between carotid IMT and diameter with other potential predictors, including age, sex, pubertal stage lipoproteins, BMI and other anthropometric adiposity measures. CIMTmax was significantly associated with BMI (r=0.52, p=0.006), but not with waist or neck circumferences. CCA diameter was significantly higher in males than females as shown above. CCA diameter was associated with neck circumference (r=0.39, p=0.033) but not with any other anthropometric variables. Age, blood pressure, lipoproteins (including ApoB), fasting glucose and insulin, HOMA-IR, and hsCRP did not associate significantly with either cIMTmax or carotid diameter (all p-values>0.05, data not shown). Trends were uncovered towards associations between cIMTmax and sagittal abdominal diameter (r=0.40, p=0.050), SBP (r=0.38, p=0.065), HDL (r=0.35, p=0.073) and triglycerides (r=−0.37, p=0.057), but these did not achieve statistical significance.

Hierarchical linear regression analysis further explored the contribution of OSAS vis-à-vis obesity to cIMTmax and carotid diameter (see table 4 for listing of all variables included in regression models). The strongest correlates of cIMTmax were BMI and HDL (table 4); AHI was not a significant statistical predictor of cIMTmax on regression analysis. Neither AHI nor degree of obesity were significant correlates with CCA diameter (table 4) on regression analysis; instead, the primary (negative) correlate was mean E_TCO_2, with a secondary positive contribution to the model from male sex. BMI, age, SBP Z-score, neck circumference, waist circumference, HOMA-IR and triglycerides were not significant contributors to the CCA diameter regression model. Alternative regression models were

constructed examining the association between CCA diameter and mean E_TCO_2 to elucidate whether potential confounders (e.g. sex) could explain this negative association. Models forced entry of age and sex and (in one model) neck circumference at the first stage, and included mean E_TCO_2 and (in one model) BMI entered stepwise at the second stage. No model contained more than 4 variables. Mean E_TCO_2 remained the strongest correlate of CCA diameter; only sex contributed to any regression model (data not shown).

B. PREDICTORS OF CFPWV AND AIx—Significant associations were seen between CFPWV and BMI (r=0.45, p=0.01), age (r=0.42, p=0.02), and pulse pressure (r=0.39, p=0.04). The relationship between BMI and CFPWV is depicted in figure 2. No relationship was seen between CFPWV and any primary OSAS measure (table 3); of the secondary OSAS measures examined, only lowest sleeping heart rate correlated with CFPWV (correlation coefficient = −0.425, p=0.019). No relationship was seen between CFPWV and fasting insulin or glucose, HOMA-IR, MAP, HR, SBP, DBP or their Z-scores, lipoproteins, ApoB, or hsCRP (all p-values>0.05, data not shown).

BMI trended towards associating negatively with AIx (r=−0.35, p=0.055). Other variables associated with AIx included SBP (r=−0.66, p<0.0005), SBP Z-score (r=−0.43, p=0.015), pulse pressure (r=−0.49, p=0.006), MAP (r=−0.40, p=0.026), fasting insulin (r=−0.56, p=0.001) and HOMA-IR (r=−0.53, p=0.002). No primary or secondary OSAS measure was significantly associated with the AIx. No significant associations were seen between AIx and age, HR, DBP and DBP Z-score, lipids, ApoB, hsCRP or fasting glucose (data not shown).

Hierarchical linear regression analysis further explored the contribution of OSAS vs. obesity to CFPWV and central pressure augmentation. The most significant (positive) correlate of CFPWV was BMI, followed by age. AHI was not a significant correlate of CFPWV (table 4) on regression analysis. Only HOMA-IR was a significant correlate of AIx; neither BMI nor AHI were significant statistical predictors of AIx on regression analyses (table 4).

Discussion

In this study, we examined the relative contributions of obesity vs. OSAS to indices of macrovascular structure and function related to CVD risk among obese adolescents. We found that BMI was the primary predictor of carotid IMT (a measure of carotid structural changes and a surrogate measure of subclinical atherosclerosis in adults) and CFPWV (a measure of large artery stiffness); OSAS was not an independent predictor. The strongest predictor of the AIx, adjusting for heart rate, was insulin resistance (HOMA-IR), whereas the primary determinants of CCA diameter were mean E_TCO_2 and sex. HDL was a minor predictor of cIMTmax, but no other relationships were found between lipoproteins (including ApoB), fasting glucose and hsCRP and most CVD risk measures examined. SBP was negatively associated with AIx, but the association was attenuated after considering the contributions of insulin resistance and obesity.

While a number of adult studies have linked OSAS with CVD burden, showing an association with atherosclerosis(12), arterial stiffness(32), and cardiovascular events(14)

and/or showing risk reduction with continuous positive airway pressure therapy(33), others have reported no independent association between OSAS and CVD risk independent of obesity(34) or no reduction of CVD risk with OSAS treatment(35). Thus, while OSAS may well increase CVD risk in adults, its impact may be difficult to disentangle from contributions of obesity. Also, studies of adults, who could have suffered from OSAS for decades, may not be directly applicable to adolescents.

Several pediatric studies have shown that carotid IMT is elevated in patients with obesity(36), hypertension and dyslipidemia(37). However, the only study that (to our knowledge) has examined carotid IMT vis-à-vis OSAS in children found no association between OSAS and IMT(38). Our results are in line with those reported by Dubern *et al*(38), despite incorporating additional predictive factors such as pubertal stage and measures of inflammation and dyslipidemia. In contrast, OSAS in children has been independently associated with endothelial dysfunction which was reversible upon OSAS treatment (adenotonsillectomy)(17). Endothelial injury and consequent dysfunction play an important role in atherogenesis(39); endothelial dysfunction is an early vascular disease marker, detectable well before structural changes can be observed(39). This lag between the development of endothelial dysfunction and macrovascular changes may explain the lack of association between AHI and cIMTmax in our study population.

The relationship between OSAS and arterial stiffness has only been examined in one pediatric study of which we are aware. Dubern and colleagues found no association between OSAS and flow-mediated dilatation (FMD) (measuring post-ischemia vasodilatation), but did report that glyceryl trinitrate (GTN)-mediated brachial artery dilatation (endothelium-independent vasodilatation) was greater in children with more significant nocturnal oxyhemoglobin desaturation(38), which the authors attributed to baseline brachial vasoconstriction in response to chronic hypoxemia. To our knowledge, no previous pediatric study has examined the independent contribution of OSAS to pulse wave velocity or the augmentation index. CFPWV reflects a different aspect of vascular damage than either FMD or IMT(40), since it is directly related to arterial wall stiffness, rather than muscular artery endothelial function. In our study, obesity was the primary correlate of PWV, rather than AHI or gas exchange abnormalities during sleep. Our study suggests that large artery stiffening either is not independently associated with OSAS in children, or that the large artery stiffness in response to chronic oxidative stress reported in adults(41) may take many years to develop. Our study participants with OSAS may not have had the condition for long enough to accrue sufficient damage so as to cause clinically detectable results on PWV or AIx analyses.

In our study, the contribution of insulin resistance to the AIx outweighed contribution of obesity. The association between insulin resistance and AIx has been reported in adolescents previously by Urbina and colleagues(42), but our study is the first to our knowledge to examine the relative contribution of insulin resistance vs. OSAS to AIx. Insulin is a known vasodilator; vasodilatation due to chronic hyperinsulinemia is the likeliest explanation for the lower AIx in individuals with higher values of HOMA-IR. The relationships between insulin resistance and vascular dysfunction should be further explored in children, with examination of the potential role of the SNS and RAA axis.

Our most intriguing finding was the negative relationship between mean asleep E_TCO_2 and common carotid artery diameter. As CO_2 is a known vasodilator, especially of cerebral arteries(43), this negative relationship was unanticipated. The association between E_TCO_2 and CCA diameter appeared to be independent of both OSAS and obesity, as neither the OSAS measures examined (AHI, sleep fragmentation, oxyhemoglobin desaturation) nor BMI predicted CCA diameter on regression analysis. Colinearity from sex and neck circumference was excluded as a possible explanation, since secondary regression analyses showed no contribution from neck circumference and showed that E_TCO_2's contribution outweighed that of sex. Contribution from obesity-related hypoventilation cannot be excluded, but as only 2 participants met criteria for hypoventilation, this possibility could not be explored further in our cohort. This negative association may relate to hypercapnia-mediated increased SNS activity(41), which in turn activates the RAA axis(44). Angiotensin II activates NADPH oxidase and enhances superoxide production at the expense of nitric oxide (NO) synthesis(45). Decreased NO production can impair vasodilatation and lead to endothelial dysfunction(45). We speculate that chronic nocturnal hypercapnia may lead to some degree of NO depletion and, over time, decreased carotid dilatation. Alternatively, chronic hypercapnia could (initially) lead to cerebral vasodilatation. In the context of stiffened central arteries, this vasodilatation could facilitate transmission of pulsatile energy into the cerebral microcirculation, which if sustained can lead to microvascular damage, as has been seen in older adults(46). We speculate that compensatory carotid artery narrowing could occur as a cerebroprotective adaptation. This relationship should be further explored in future studies with a larger sample size, and expanding the age range to include young adults.

Our study should be interpreted in the context of its strengths and limitations. We examined a large number of well-validated indices of CVD risk (cIMTmax, carotid diameter, PWV), and examination of contribution of all sex, pubertal status, metabolic syndrome components (waist circumference, BP, triglycerides, HDL, fasting insulin/glucose), other lipoproteins, and inflammation upon the primary relationships of interest. Although our sample size was modest, we were powered to identify correlation coefficients between AHI and outcomes of interest of 0.49 or greater; this is in the range of the correlation coefficients reported in adults between AHI and both cIMTmax and PWV(47). Our study also had some limitations. Our cohort was primarily normotensive and non-dyslipidemic, which may have limited our ability to assess the impact elevated BP or dyslipidemia upon CVD risk. Some studies have found that not every child with OSAS is equally susceptible to its metabolic sequelae(48). Thus, although our participants exhibited a range of OSAS severity, our population could possibly have contained a larger subset of such resistant children. A larger sample size might have allowed more subtle relationships to emerge. Finally, it should be noted that total rather than central adiposity was the primary determinant of macrovascular measurements. Of note, BMI was used in preference to BMI Z-score as the measure of overall obesity because of BMI Z-score's known limitation in obese populations such as this - BMI percentiles are skewed at the higher end, with a wide BMI range becoming compressed into a narrow range of BMI Z-scores(49).

In conclusion, we found that in a cohort of obese adolescents, the primary predictor of measures of carotid structure changes and arterial stiffness was the degree of obesity rather

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than OSAS. We speculate that the vascular damage wrought by OSAS takes years to manifest, and thus is infrequently seen in pediatric populations. Future studies should involve a larger cohort of adolescents, and should also examine measures of endothelial function (NO-mediated and not) to assess whether endothelial dysfunction may be the link between OSAS in children and the vascular changes reported in adults. Future studies should also assess the impact of SNS activity and possibly the RAA axis upon the outcomes of interest.

Acknowledgments

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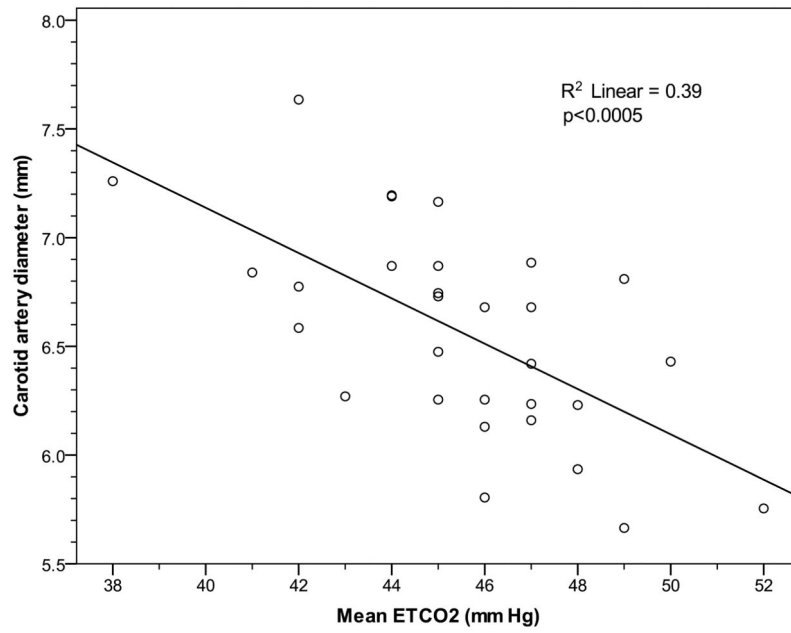
Figure 1. Relationship between carotid artery diameter and end-tidal CO_2
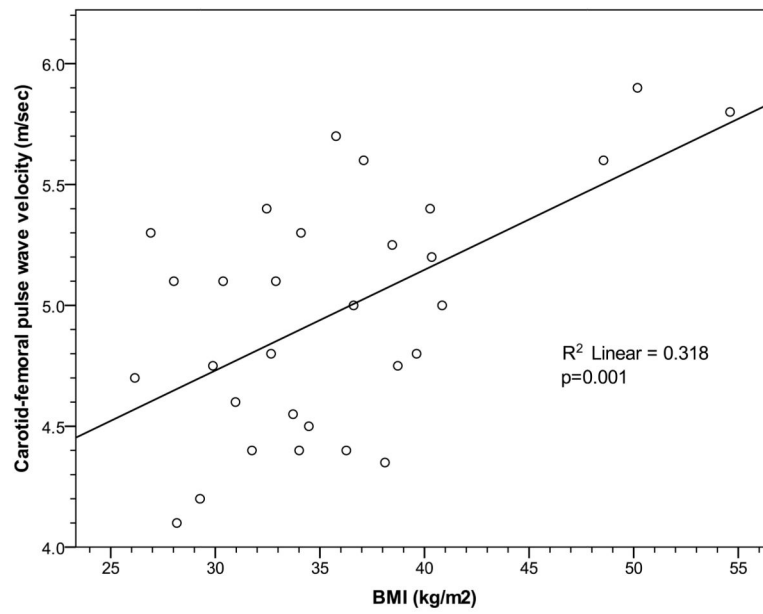Association between common carotid artery diameter and mean end-tidal carbon dioxide.

Figure 2. Relationship between obesity and pulse wave velocity
Association between degree of obesity and carotid-femoral pulse wave velocity. BMI=body mass index.

Table 1

Baseline subject characteristics and anthropometric measurements

Characteristic	Mean ± S.D. or N (%)
N	31
Age (years)	14.7 ± 1.8
Male Sex	19 (61%)
Tanner Stage:	
Tanner 2	3 (10%)
Tanner 3	2 (7%)
Tanner 4	4 (13%)
Tanner 5	22 (71%)
Height (cm)	168.8 ± 8.6
Weight (kg)	102.3 ± 22.5
BMI (kg/m2)	35.8 ± 6.6
BMI Z-score	2.32 ± 0.40
Waist circumference (cm)	108.7 ± 16.1
Sagittal abodminal diameter (cm)	24.2 ± 2.25
Neck circumference (cm)	40.4 ± 2.7

BMI=body mass index; cm=centimeter; m=meter; kg=kilogram; S.D.= standard deviation.

Table 2

Polysomnography and cardiovascular risk measure results

Characteristic	Mean ± S.D. or N (%)	Median (interquartile range)*
Sleep measures		
TST (minutes)[†]		439 (420, 472)
Arousal index (events/hour sleep)[†]	11.5 ± 9.4	9 (5, 12)
SpO_2 nadir (%)[†]	87.2 ± 8.7	91 (83, 93)
Mean SpO_2 (%)	97.0 ± 1.1	
AHI (events/hour sleep)[†] Distribution: AHI <1.5 AHI 1.5–<5 AHI 5–<10 AHI 10	11.0 ± 17.3 N = 4 (13%) N = 16 (51%) N = 3 (10%) N = 8 (26%)	2.8 (1.7, 12.2)
Peak E_TCO_2 (mm Hg)	54.3 ± 4.5	
Mean E_TCO_2 (mm Hg)	45.5 ± 2.8	
Time E_TCO_2 >50 torr (% TST)[†]		1 (0, 13)
Primary (imaging) cardiovascular risk outcome measures		
Maximal carotid IMT (cIMTmax; mm)	0.51 ± 0.06	
CCA diameter (mm)	6.56 ± 0.48	
CFPWV (m/sec)	5.0 ± 0.5	
Augmentation index (AP/PP)	−32.87 ± 12.76	
Other cardiovascular risk outcome measures		
i. Biochemical:		
Total cholesterol (mmol/L)	3.78 ± 0.67	
HDL cholesterol (mmol/L)	1.17 ± 0.28	
Triglycerides (mmol/L)	1.89 ± 0.78	
LDL cholesterol (mmol/L)	2.20 ± 0.54	
Non-HDL cholesterol (mmol/L)[†]		2.56 (2.12, 2.87)
Apolipoprotein B (g/L)	0.69 ± 0.15	

Characteristic	Mean ± S.D. or N (%)	Median (interquartile range)*
High-sensitivity CRP (nmol/L)[†]		15.91 (7.43, 69.33)
Fasting glucose (mmol/L)	5.05 ± 0.28	
Fasting insulin (pmol/L)[†]		139.2 (110.5, 215.3)
HOMA-IR[†]		4.5 (3.2, 6.5)
ii. Blood pressure:		
SBP (mm Hg)	112 ± 10	
DBP (mm Hg)	60 ± 5	
Pulse pressure (mm Hg)	53 ± 10	
Mean arterial pressure (mm Hg)	77 ± 4.9	
Systolic Blood Pressure Z-score	−0.87 ± 0.94	
Diastolic Blood Pressure Z-score		−0.6 (−0.8, −0.3)

[†]Non-normally distributed variable. Median and percentiles given for non-normally-distributed variables only

Legend: TST=total sleep time; AHI=apnea-hypopnea index; E_TCO_2=end-tidal CO_2; IMT=intima-media thickness; CCA=common carotid artery; CFPWV=carotid-femoral pulse wave velocity; AP=augmentation pressure; PP=pulse pressure; CRP=C-reactive protein; HDL=high-density lipoprotein; LDL=low-density lipoprotein; HOMA-IR=homeostasis model assessment of insulin resistance

Table 3

Correlation coefficients between obstructive sleep apnea syndrome measures and primary imaging cardiovascular risk markers

	AHI[†]	Arousal Index[†]	SpO₂ nadir[†]	Mean SpO₂	Peak sleep E_TCO₂	Mean sleep E_TCO₂
cIMTmax	0.02 (0.91)	0.03 (0.89)	−0.27 (0.17)	0.24 (0.23)	0.14 (0.50)	0.12 (0.55)
CCA diameter	0.07 (0.70)	−0.01 (0.95)	0.04 (0.83)	−0.18 (0.32)	0.28 (0.13)	**−0.625 (<0.0005)**
CFPWV[†]	0.16 (0.40)	0.29 (0.12)	−0.02 (0.93)	−0.17 (0.38)	−0.13 (0.48)	−0.19 (0.31)
AIx (AP/PP)	0.01 (0.96)	−0.03 (0.88)	0.24 (0.20)	0.24 (0.10)	0.11 (0.55)	0.01 (0.95)

Numbers represent Pearson correlation coefficients unless otherwise noted.

[†] Spearman correlation analysis. Numbers in bold indicate significant association.

Legend: CFPWV= carotid-femoral pulse-wave velocity; CCA=common carotid artery; cIMTmax = mean maximal carotid intima-media thickness; AIx=augmentation index (AP/PP); SpO2=oxyhemoglobin saturation.

Table 4

Regression Analyses – correlates of cardiovascular disease risk measures

	R² change	R² change p-value	Variable Std β-coeff.	β-coeff. p-value	Overall model adjusted R²	Overall model p-value
Maximal carotid IMT						
BMI entered	0.191	0.026	0.593	0.004	0.157	0.026
After BMI, LN_AHI (forced entry) adds:	0.056	0.203	−0.171	0.365	0.182	0.038
After BMI&LN_AHI, HDL (step-wise) adds	0.166	0.021	0.424	0.021	0.333	0.007
Carotid artery diameter						
BMI entered	0.02	0.463	−0.069	0.666	−0.016	0.463
After BMI, LN_AHI (forced entry): NO VARIABLES ENTERED MODEL *	0.021	0.457	0.023	0.8898	−0.033	0.579
After BMI&LN_AHI, mean E_TCO_2 (stepwise) adds:	0.364	0.001	−0.562	0.001	0.334	0.004
After BMI, LN_AHI& mean E_TCO_2, male sex adds:	0.127	0.018	0.385	0.018	0.454	0.001
CFPWV						
BMI entered	0.29	0.003	0.64	0.001	0.26	0.03
After BMI, LN_AHI (entered) adds:	0.003	0.76	−0.14	0.41	0.24	0.012
After BMI&LN_AHI, Age (step-wise) adds:	0.17	0.01	0.42	0.01	0.39	0.001
Augmentation index AP/PP (AIx)						
BMI entered	0.125	0.056	−0.117	0.602	0.093	0.056
After BMI, LN_AHI (entered) adds:	0.005	0.698	−0.038	0.844	0.065	0.153
After BMI&LN_AHI, LN_HOMA-IR (stepwise) adds:	0.136	0.037	−0.442	0.037	0.181	0.043

Additional variables incorporated into serial secondary regression models which were not significant predictors:

• CIMTmax: After BMI, LN_AHI and HDL, serial secondary models included the following non-significantly-contributing variables in turn: SBP Z-score, age, TGs, waist circumference, LN_HOMA-IR, sagittal abdominal diameter.

• CCA diameter: After BMI, LN_AHI, mean ETCO2: age, TGs, SBP-z-score, neck circumference, waist circumference, LN_HOMA-IR.

• CFPWV: After BMI, LN_AHI, and age: HR (awake), lowest asleep HR, SBP Z-score, MAP, sex, waist circumference, LN_HOMA-IR.

• AIx: After BMI, LN_AHI, and LN_HOMA-IR: age, HR, MAP, SBP Z-score, pulse pressure, waist circumference.

* No variables entered – neither BMI nor LN_AHI were significant predictors of CCA diameter

Legend: CFPWV= carotid-femoral pulse-wave velocity; CCA=common carotid artery cIMTmax = maximal carotid intima-media thickness; AIx=augmentation index (AP/PP); BMI=body mass index; AHI=apnea hypopnea index; LN=natural log; E$_T$CO2=end-tidal CO2; HDL=high-density lipoprotein; SBP=systolic blood pressure; HOMA-IR=homeostasis model assessment of insulin resistance; HR=heart rate; MAP=mean arterial pressure; TGs=triglycerides