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SCIENTIFIC INVESTIGATIONS

Prevalence of pulmonary hypertension on echocardiogram in children with severe obstructive sleep apnea

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Study Objectives: Pulmonary hypertension (PH) is a rare yet serious complication of obstructive sleep apnea (OSA). Echocardiographic screening for PH is recommended in children with severe OSA, but the health care burden of universal screening is high. We sought to determine the prevalence of PH on echocardiogram among children with severe OSA and identify variables associated with a positive PH screen.

Methods: Retrospective study of 318 children with severe OSA (obstructive apnea-hypopnea index ≥ 10 events/h) and echocardiogram within 1 year of polysomnogram. PH-positive echocardiogram was defined by peak tricuspid regurgitation velocity ≥ 2.5 m/s and/or 2 or more right-heart abnormalities suggestive of elevated pulmonary artery pressure. Patient characteristics and polysomnogram data were compared to identify factors associated with PH.

Results: Twenty-six children (8.2%; 95% confidence interval [CI] 5.4–11.8%) had echocardiographic evidence of PH. There was no difference in age, sex, body mass index, obstructive apnea-hypopnea index, or oxygenation indices between patients with and without PH. Sleep-related hypoventilation (end-tidal CO_2 > 50 mmHg for > 25% of total sleep time) was present in 25% of children with PH compared with 6.3% of children without PH (adjusted prevalence ratio = 2.73; 95% CI 1.18–6.35). Forty-six percent of children (12/26) with PH had Down syndrome vs 14% (41/292) without PH (adjusted prevalence ratio = 3.11; 95% CI 1.46–6.65).

Conclusions: There was a relatively high prevalence of PH on echocardiogram in our cohort of children with severe OSA. The findings of increased PH prevalence among children with sleep-related hypoventilation or Down syndrome may help inform the development of targeted screening recommendations for specific pediatric OSA populations.

Keywords: obstructive sleep apnea, pulmonary hypertension, echocardiogram, pediatrics

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Pulmonary hypertension (PH) is a rare yet serious complication of obstructive sleep apnea (OSA). Current guidelines recommend that children with severe OSA undergo PH screening by echocardiogram but screening all children with severe OSA may be costly and impractical in many health care settings. We retrospectively studied a cohort of children with severe OSA to determine the prevalence of PH on echocardiogram and identify patient characteristics and polysomnogram variables associated with positive PH screen.

Study Impact: Twenty-six of 318 children with severe OSA had echocardiogram findings suggestive of PH. Children with hypoventilation on polysomnogram or a history of Down syndrome were more likely to have evidence of PH on echocardiogram. These populations may warrant consideration for prioritized PH screening.

INTRODUCTION

Pediatric obstructive sleep apnea (OSA) is defined by partial or complete airway obstruction during sleep, resulting in impaired gas exchange, recurrent arousals, and disruption of normal sleep architecture.[1–3] OSA is seen frequently in the general pediatric population, with an estimated prevalence of 1.2–5.7%.[1] Prevalence is increased in children with adenotonsillar hypertrophy, obesity, and chronic medical conditions such as Down syndrome (DS), Prader-Willi syndrome, neuromuscular disease, and craniofacial disorders. Untreated pediatric OSA may be associated with daytime behavioral impairment, neurocognitive deficits, metabolic derangements, systemic inflammation, and cardiovascular dysfunction.[1,3–5]

Cardiovascular complications of OSA in children include systemic blood pressure dysregulation, biventricular dysfunction, and pulmonary hypertension (PH).[1,3–11] PH is particularly worrisome as it may lead to right-heart failure and significant morbidity.[12,13] PH is rare in children and prevalence estimates among pediatric patients with OSA vary widely.[11,14–18] The risk of PH in children with OSA is thought to increase with OSA severity[8,19] and echocardiographic screening for PH is recommended in children with severe OSA.[20] Children with OSA and certain genetic syndromes such as DS may be at increased risk for developing PH,[11,21] but other specific risk factors for PH in pediatric OSA have not been well delineated.

Early identification of PH in children with OSA is important since effective OSA treatment can improve or even normalize

elevated pulmonary artery pressures.[11,22] However, echocardiographic screening of all patients with severe OSA for PH is costly and may be impractical in many health care settings. A better understanding of the prevalence of PH in children with severe OSA and identification of PH risk factors could inform future screening recommendations and help providers prioritize testing for those at highest risk when resources are limited. We retrospectively studied a cohort of pediatric patients with severe OSA and who had undergone echocardiographic evaluation to determine the prevalence of PH in this cohort and identify patient characteristics or polysomnogram (PSG) features associated with the presence of PH on echocardiogram.

METHODS

Study design and population

This single-center, retrospective cohort study was completed at Children's Hospital Los Angeles, an urban pediatric tertiary care center, based on review of patient records from January 1, 2011, to December 31, 2018. The study was approved by the Children's Hospital Los Angeles Institutional Review Board. A query of the electronic health records using procedure codes for PSG and echocardiogram was used to identify children ages 2–17 years who had a PSG and echocardiogram within 1 year of each other. PSG reports were reviewed to identify children with severe OSA (defined by an obstructive apnea-hypopnea index [OAHI] ≥ 10 events/h). Patients whose sleep study did not include a diagnostic portion (eg, full-night oxygen or positive airway pressure titration) were excluded. We excluded patients with missing or incomplete documentation of PSG or echocardiogram results, or if the echocardiogram report stated that there was insufficient information to evaluate right ventricular or pulmonary artery pressures. Additional exclusion criteria included acute cardiorespiratory failure at the time of PSG or echocardiogram, tracheostomy status, or history of cyanotic congenital heart disease (CHD).

Data collection and outcomes

Data were collected from review of the electronic health record. Demographic data included sex and age at time of PSG. Height, weight, and body mass index (BMI) values were documented. Based on BMI percentile for age and sex, participants were categorized as underweight (< 5th percentile), normal weight (5th to < 85th percentile), overweight (85th to < 95th percentile), or obese (≥ 95th percentile). Obese children were further subclassified as obese (BMI ≥ 95th percentile but < 120% of the 95th percentile) or severely obese (BMI ≥ 120% of the 95th percentile).[23,24] Information on chronic conditions and past medical history was recorded.

PSG data were obtained from existing reports. PSGs were conducted and scored by pediatric parameters in accordance with the most contemporary version of *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*.[25] PSG variables recorded included OAHI, central apnea index, arousal index, baseline oxygen saturation (SpO_2), SpO_2 nadir, number of oxygen desaturation events per hour (oxygen desaturation index) with desaturation defined as drop in SpO_2 by ≥ 3%, proportion of total sleep time (TST) with SpO_2 < 90%, peak end-tidal carbon dioxide ($P_{ET}CO_2$) measurement, proportion of TST with $P_{ET}CO_2$ > 50 mmHg, and presence of hypoventilation ($P_{ET}CO_2$ > 50 mmHg for > 25% of TST).

Echocardiogram data were collected from existing standardized echocardiogram reports and included information on peak tricuspid regurgitation velocity (TRV; m/s) and presence of right-heart abnormalities associated with elevated pulmonary artery pressure (PAP) such as right atrial dilation, right ventricular (RV) dilation, RV hypertrophy, abnormal interventricular septal geometry, pulmonary artery dilation, or significant pulmonary valve regurgitation. Any other abnormal findings documented by the echocardiogram report were also recorded.

The primary outcome was the presence of echocardiogram findings suggestive of PH. Pediatric PH is defined by a mean PAP > 20 mmHg at sea level as measured by cardiac catheterization.[26–28] Doppler echocardiography is a validated noninvasive means to evaluate right-heart pressures and pulmonary hemodynamics and is the most common method to screen for PH in children. In the absence of RV outflow tract obstruction, systolic PAP is equivalent to RV systolic pressure and can be calculated through application of the modified Bernoulli equation to the Doppler-determined peak TRV.[29,30] As mean PAP = (0.61 × systolic PAP) + 2, a systolic PAP ≥ 30 mmHg approximately corresponds to a mean PAP > 20 mmHg, suggesting the presence of PH.[30,31] Individuals with a TRV ≥ 2.5 m/s and/or 2 or more abnormal right-heart characteristics were categorized as having evidence of PH on echocardiogram.

Statistical analysis was performed using STATA statistical software v17.1 (StataCorp, College Station, TX). Categorical variables were expressed as counts or percentages while continuous variables were expressed as medians/interquartile ranges. Children with PH were compared with those without evidence of PH on echocardiogram. Categorical data were compared by 2-tailed Fisher's exact test. Continuous variables were analyzed by Wilcoxon rank-sum test. Statistical significance was defined as alpha (α) ≤ 0.05. A variable selection algorithm was implemented to select the factors associated with PH.[32] A multivariate generalized linear model (log link and binomial family)[33] was applied to estimate the effect of these factors on PH adjusted for covariates and to calculate the covariate-adjusted PH prevalence ratio. Pearson correlation was used to evaluate for associations between TRV and continuous PSG variables.

RESULTS

From 2011 through 2018, 1,406 encounters for children who had a PSG and echocardiogram within 1 year were identified. Ninety records were excluded due to missing or insufficient documentation of PSG or echocardiogram. PSG reports were reviewed to exclude patients who had a PSG without a diagnostic portion (n = 167) or OAHI of less than 10 events/h (n = 759). The remaining participants' medical records were examined. Sixty children were excluded due to the presence of acute cardiorespiratory failure, tracheostomy status, or history of cyanotic CHD.

Nine patients had multiple encounters for PSG and echocardiogram. For these patients we selected the first instance of positive echocardiogram screen or, if patients had no positive screen, data were collected from the earliest encounter within the study time frame.

A total of 318 pediatric patients with severe OSA and echocardiogram met the criteria and were included in the study. A total of 232 patients underwent echocardiogram after PSG and 86 patients had an echocardiogram prior to PSG. The median age was 9.6 years (interquartile range 5.2–14.2 years) (**Table 1**). The male-to-female ratio was 2.5:1. Over half of the patients (56.3%; n = 179) were obese and 63.7% of obese children were severely obese. Approximately one-third of children (34.6%; n = 110) had no reported comorbid medical conditions other than obesity (71.8%; n = 79). Patients with additional diagnoses were categorized by primary medical condition. The most common conditions were neuromuscular disease (22%; n = 70), DS (16.7%; n = 53), and craniofacial disorders (4.1%; n = 13). The

Table 1—Patient demographics, polysomnogram data, and comorbid conditions.

	All Patients (n = 318)	Without PH (n = 292)	With PH (n = 26)	*P*
Age, y	9.6 (5.2–14.2)	9.9 (5.2–14.3)	8.8 (4.6–13.3)	.552
Male	71.1% (226)	70.5% (206)	76.9% (20)	.653
BMI *z*-score	1.8 (−0.15 to 2.4)	1.8 (0.3–2.6)	2.1 (0.7–2.7)	.197
BMI category*				
Underweight	8.2% (26)	8.9% (26)	0% (0)	.472
Normal weight	25.5% (81)	25.3% (74)	26.9% (7)	
Overweight	10.1% (32)	10.3% (30)	7.7% (2)	
Obese	56.3% (179)	55.5% (162)	65.4% (17)	
Obese	20.4% (65)	20.2% (59)	23.1% (6)	1.000
Severely obese	35.8% (114)	35.3% (103)	42.3% (11)	
Polysomnogram data				
OAHI, events/h	23.4 (15.5–46.0)	23.2 (15.5–42.6)	28.1 (14.3–64.5)	.622
CAI, events/h	0.9 (0.2–3.2)	0.9 (0.2–3.2)	0.9 (0.3–2.6)	.933
ODI, events/h	24.7 (15.0–46.6)	24.7 (15.0–46.6)	24.1 (13.1–49.4)	.996
SpO_2 baseline, %	95 (93–96)	95 (93–96)	94.5 (92.8–96)	.384
SpO_2 nadir, %	78 (69–85)	78.5 (69–85)	74 (66–84)	.303
TST SpO_2 < 90%, %	4.1 (1–11.4)	4.0 (1–11.4)	4.9 (1.1–11.16)	.790
Peak $P_{ET}CO_2$, mmHg	53 (48.3–57)	53 (48.3–56)	55 (48.5–62)	.200
TST $P_{ET}CO_2$ > 50 mmHg, %	0 (0–2.3)	0 (0–2)	0.4 (0–25)	.090
Hypoventilation†	7.8% (24)	6.4% (18)	25.0% (6)	.006
Arousal index, events/h	18.6 (11.0–28.8)	18.6 (11.1–28.8)	19.3 (9.4–28.1)	.555
Primary medical diagnosis				
No major comorbidity	34.6% (110)	36.6% (107)	11.5% (3)	.009
Other	22.6% (72)	21.2% (62)	38.5% (10)	.052
Neuromuscular disease	22.0% (70)	24.0% (70)	0% (0)	.002
Down syndrome	16.7% (53)	14.0% (41)	46.2% (12)	< .001
Craniofacial	4.1% (13)	4.1% (12)	3.8% (1)	1.000
Other comorbid conditions				
History of prematurity‡	17.8% (53)	17.6% (48)	20.8% (5)	.780
History of CHD	14.5% (46)	11.6% (34)	46.2% (12)	< .001
Current CHD	4.4% (14)	3.1% (9)	19.2% (5)	.003
Resolved CHD	10.1% (32)	8.6% (25)	26.9% (7)	.009

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as percentage (count). *P* values were calculated by Wilcoxon rank-sum test (continuous variables) or Fisher's exact test (categorical variables). *BMI category is defined by underweight (< 5th percentile), normal weight (5th to < 85th percentile), overweight (85th to < 95th percentile), or obese (≥ 95th percentile). Obese patients were further classified as obese (BMI ≥ 95th percentile but < 120% of the 95th percentile) or severely obese (BMI ≥ 120% of the 95th percentile). †Eleven children (9 without PH, 2 with PH) had insufficient capnography data to assess for hypoventilation. ‡Information on prematurity or gestational age at birth was unavailable for 21 patients (19 without PH, 2 with PH). BMI = body mass index, CAI = central apnea index, CHD = congenital heart disease, OAHI = obstructive apnea-hypopnea index, ODI = oxygen desaturation index, $P_{ET}CO_2$ = peak end-tidal carbon dioxide, PH = pulmonary hypertension, SpO_2 = oxygen saturation, TST = total sleep time.

remaining 72 patients (22.6%) had a heterogeneous array of genetic or acquired conditions, including various metabolic or endocrine disorders (n = 13), Prader-Willi syndrome (n = 7), liquid or solid malignancies (n = 7), sickle cell disease (n = 4), rheumatologic disease (n = 4), renal disease (n = 4), bronchiectasis (n = 2), and other congenital disorders or acquired upper airway conditions.

Forty-six patients (14.5%) had a history of current (n = 14) or past (n = 32) noncyanotic CHD. Among patients with current CHD lesions, 1 patient had mild mitral valve regurgitation and mitral valve cleft, 5 had a small or moderate atrial septal defect (ASD), 4 had a small ventricular septal defect (VSD), 1 had a moderate VSD, 2 had a small VSD and ASD, and 1 had a large VSD and moderate ASD. Lesions in children with resolved CHD included ASD (n = 10), VSD (n = 3), ASD and VSD (n = 8), atrioventricular canal (n = 4), patent ductus arteriosus requiring surgical closure (n = 3), coarctation of the aorta and VSD (n = 1), Ebstein anomaly (n = 1), anomalous coronary artery (n = 1), and vascular ring (n = 1). The majority of patients with CHD had DS (31/46; 67%) and 58.5% (31/53) of patients with DS had a history of CHD. Six patients with Duchenne muscular dystrophy had mild to moderate dilated cardiomyopathy. Isolated mild left ventricular dilation was noted in one 15-year-old male with severe obesity. Five patients carried a diagnosis of systemic hypertension but had no abnormalities on echocardiogram.

Twenty-six children (8.2%; 95% confidence interval [CI] 5.4–11.8%) had evidence of PH on echocardiogram (**Table 2**). Two patients had a pre-existing diagnosis of PH: a 5-year-old girl with DS and Eisenmenger syndrome associated with a large unrepaired VSD and a 14-year-old boy with granulomatosis with polyangiitis. Peak TRV could not be measured in 151 children. No children without a measurable TRV had 2 or more right-heart abnormalities on echocardiogram.

Pearson correlation coefficients were calculated for the 167 patients with measurable peak TRV. We found no significant correlation between peak TRV and OAHI ($r = .06$, $P = .41$), ODI ($r = .01$, $P = .92$), SpO_2 nadir ($r = -.08$, $P = .30$), %TST $SpO_2 < 90\%$ ($r = .09$, $P = .26$), or %TST $P_{ET}CO_2 > 50$ mmHg ($r = .14$, $P = .08$).

A comparison of anthropometric measures, PSG data, and comorbid health conditions between patients with and without evidence of PH is shown in **Table 1**. Sleep-related hypoventilation was present in 25% of children with PH compared with 6.4% of children without PH ($P = .006$, adjusted prevalence ratio = 2.73; 95% CI 1.18–6.35). There was no association between hypoventilation and central sleep apnea, suggesting that hypoventilation was primarily obstructive in nature. Patients with neuromuscular disease or no major comorbidity were less likely to have evidence of PH on echocardiogram. Twelve of 53 children (22.6%) with DS had PH (adjusted prevalence ratio 3.11; 95% CI 1.46–6.65). Both DS and CHD were associated with the presence of PH on echocardiogram, but there was significant overlap within these patient populations. Over half (53.8%; 14/26) of children with PH had a history of DS (n = 2), CHD (n = 2), or both (n = 10). Among patients with DS, PH was present in 10 of 31 children (32.3%) with a history of CHD, compared with 2 out of 22 (9.1%) without a history of CHD, but this difference was not statistically significant ($P = .093$) Of the 15 children who did not have DS but had a history of CHD, 2 (13.3%) had PH on echocardiogram. There was insufficient power to draw meaningful conclusions regarding the association between CHD and PH in children without DS.

DISCUSSION

In this cohort of children with severe OSA, 8.2% had echocardiographic evidence of PH. There was a high prevalence of obesity and comorbid medical conditions among our study population. We found no relationship between OAHI or degree of hypoxemia and PH but did find an association between PH and the presence of hypoventilation on PSG. PH prevalence was increased among children with DS.

Case reports of children with upper airway obstruction leading to PH and cor pulmonale date back over 50 years,[34] but there have been few large-scale studies examining the prevalence of PH in children with OSA. A 2017 review by Ingram and colleagues[11] summarized the available literature on OSA and PH in children. PH prevalence estimates varied widely from 0 to 85%, likely due to small sample sizes, methodological differences in PH assessment, and reliance on clinical symptoms rather than polysomnography to establish OSA diagnosis.[11] Recently, additional studies on cardiac abnormalities in children with OSA diagnosed by PSG and managed with surgery have been published.[15–17] Teplitzky et al[16] recorded presurgical echocardiogram data from 47 children with very severe OSA (apnea-hypopnea index ≥ 30 events/h) treated with adenotonsillectomy and failed to identify significant echocardiographic abnormalities. Imaging assessment of the right heart was limited, and noninvasive estimation of RV pressure and PAP was not included. Children with unrepaired CHD or neuromuscular disease were excluded. Pettitt-Schieber et al[15] studied 110 pediatric patients with OSA (60% of whom had severe OSA) who underwent echocardiogram before upper airway surgery. Children with neuromuscular disorders were excluded. Forty-five participants had an abnormal echocardiogram, but of these 45 children, 43 had CHD. The authors found no association between PSG results and echocardiogram findings after adjustment for CHD. PH was present in 1 patient with existing diagnosis of persistent PH and congenital heart block. The echocardiographic criteria used to define PH were not specified. Clements and colleagues[17] reported 358 patients with severe OSA who underwent adenotonsillectomy. Only 43 patients had a preoperative echocardiogram, 44% of which were abnormal. The authors found no association between PSG indices and echocardiographic abnormalities. PH was identified a 3-year-old patient with Prader-Willi syndrome, obesity, repaired ASD, and OAHI of 138.5 events/h. The authors did not specify what echocardiographic parameters defined the presence of PH.

Many children with OSA are not candidates for surgical OSA treatment due to the absence of adenotonsillar hypertrophy, presence of multilevel airway obstruction or upper airway obstruction due to hypotonia or adiposity, and/or presence of comorbidities that increase anesthesia risk. Burns et al[14]

Table 2—Description of patients with evidence of PH on echocardiogram.

Age/Sex	BMI Percentile	Medical History	OAHI, Events/h	HV	Cardiac History*	TRV, m/s	Other Echocardiogram Abnormalities
2 y/M	76	Prematurity (28 weeks)	64.4	+	—	3.2	RVH, RVD, mild RA enlargement
2 y/M	98	DS; prematurity (36 weeks)	36.4	–	ASD/VSD	2.9	Small ASD, small VSD
3 y/M	76	Prematurity (26 weeks)	11.0	–	ASD (closed)	2.7	—
4 y/M	> 99	—	25.4	–	—	3.7	RVD
4 y/M	> 99	Prader-Willi syndrome	17.6	+	—	2.6	Enlarged coronary sinus
4 y/M	99	DS	30.8	–	ASD (closed)	2.6	—
4 y/F	63	DS	14.2	N/A	VSD (repaired)	2.7	—
5 y/M	> 99	DS; prematurity (34 weeks)	23.5	N/A	ASD (closed), MV prolapse	3.3	Mild MV prolapse, mild aortic root dilatation
5 y/F	71	DS	36.0	–	PH, ASD/VSD, Eisenmenger syndrome	5.5	Small ASD, moderate–large VSD, RVH, RVD, IV septum flattening, RA enlargement, pulmonary regurgitation, dilated MPA
6 y/M	37	Craniofacial tumor	104.3	+	—	2.5	—
7 y/M	> 99	Prader-Willi syndrome	11.0	–	ASD	2.5	RVD, moderate ASD
7 y/F	99	DS	19.4	–	ASD/VSD/PDA (repaired), residual VSD	2.6	Small muscular VSD
8 y/M	93	DS	55.3	–	—	2.6	RVD, mild RA enlargement
9 y/M	73	Mitochondrial disorder	30.7	–	—	2.5	—
9 y/M	> 99	—	132.3	–	—	2.5	—
9 y/F	93	DS; prematurity (34 weeks)	10.0	–	AVC (repaired), residual VSD	2.6	Small VSD
12 y/M	96	NF1, ALL (remission)	16.8	+	—	2.5	—
12 y/M	> 99	DS	12.0	+	ASD/VSD/PDA (repaired)	2.5	—
12 y/M	99	DS	14.3	–	AVC (repaired)	2.7	Tiny VSD patch leak, mild MI, bicuspid AV
13 y/F	14	Non-CF bronchiectasis, subglottic stenosis	13.8	–	—	2.6	—
13 y/M	> 99	—	67.6	+	—	2.8	—
14 y/M	98	GPA	72.9	–	PH	3.3	IV septum flattening
15 y/M	99	Achondroplasia	74.2	–	—	2.6	—
15 y/M	97	DS	19.6	–	—	2.9	—
15 y/M	97	DS	64.6	–	ASD (closed), VSD (repaired)	2.7	Tiny residual VSD leak
16 y/F	99	Craniopharyngioma, panhypopituitarism	42.0	–	—	2.6	—

*For resolved cardiac lesions "closed" denotes defects that spontaneously regressed and "repaired" indicates surgical intervention. ALL = acute lymphocytic leukemia, ASD = atrial septal defect, AV = aortic valve, AVC = atrioventricular canal, BMI = body mass index, CF = cystic fibrosis, DS = Down syndrome, F = female, GPA = granulomatosis with polyangiitis, HV = hypoventilation, IV = interventricular, M = male, MI = mitral insufficiency, MPA = main pulmonary artery, MV = mitral valve, N/A = data on presence or absence of hypoventilation not available, NF1 = neurofibromatosis type 1, OAHI = obstructive apnea-hypopnea index, PDA = patent ductus arteriosus, PH = pulmonary hypertension, RA = right atrium, RVD = right ventricular dilation, RVH = right ventricular hypertrophy, TRV = peak tricuspid regurgitation velocity, VSD = ventricular septal defect.

examined the records of children with OSA (32% of whom had severe OSA) and some form of cardiology evaluation to determine the prevalence of PH in this population. Out of 163 patients, 144 underwent echocardiogram. Thirty-nine percent of echocardiograms were abnormal and 3 children (2%) had PH, defined by TRV > 2.8 m/s. All 3 children with PH had structural heart disease (transposition of great arteries with double-outlet RV status post repair and conduit stenosis, DS with repaired ASD/VSD/patent ductus arteriosus, and presence of subaortic membrane). None had severe OSA or significant hypoxemia on PSG. Recently, Bitners et al[18] studied a cohort of 174 patients ages 2–21 years with OSA (93% with severe OSA) and found that 4% had elevated RV pressure measured by echocardiogram. They found no association between elevated RV pressure and patient demographics, anthropometric measures, or PSG variables. Children with established cardiology care were excluded.

Our cohort of children with severe OSA had a higher prevalence of PH than other published studies. We speculate several explanations. In the current study, a PH-positive echocardiogram was defined by a TRV ≥ 2.5 m/s or the presence of 2 or more qualitative abnormalities suggestive of elevated PAP. Existing literature on TRV in healthy individuals at rest suggests TRV < 2.5 m/s to be the upper limit of normal[35–37] and TRV ≥ 2.5 m/s has been demonstrated to be a predictor of mortality in children and adults.[38–40] Current PH guidelines report that a TRV > 2.8 m/s indicates an intermediate to high probability of PH in symptomatic patients.[41,42] In the context of children with severe OSA, echocardiography is primarily used as a screening tool to identify patients at high risk of cardiovascular complications. Successful treatment of OSA often leads to improvement in or resolution of its cardiac sequelae.[10,11,43,44] Even patients with mild echocardiographic abnormalities suggestive of early or evolving PH warrant intensive management to achieve OSA control and curtail disease progression. Further investigation is needed to determine the temporal course of PH development and progression in children with OSA.

Current clinical guidelines recommend screening children with severe OSA for PH based on the presumption that children with severe OSA are at higher risk for PH than children with mild to moderate OSA. Our decision to study only patients with severe OSA was based on existing clinical guidelines recommending echocardiographic screening for PH in this population.[20] We hypothesized that children with PH would have higher OAHIs and more severe hypoxemia but did not find an association between these polysomnographic variables and elevated PAP on echocardiogram. Currently, there is no validated definition for severe OSA in children and the criterion of OAHI > 10 events/h is based on limited consensus.[45,46] While OAHI > 10 events/h may be a predictor for postoperative respiratory complications in children undergoing OSA surgery,[1,45,47,48] this cutoff has not reliably been shown to correlate with cardiac sequalae of OSA. The heterogenous development of PH in some children with OSA but not others may reflect individual differences in physiologic response to chronic airway obstruction and hypoxemia as well as the significant contribution of comorbid conditions to cardiopulmonary dysfunction. Nearly two-thirds of children in our cohort had a major comorbid medical condition, and the presence of additional PH risk factors likely contributed to the comparatively high proportion of children with PH relative to previous studies.

Among children with severe OSA, hypoventilation (defined by $P_{ET}CO_2$ > 50 mmHg for > 25% of TST) was independently associated with PH. Twenty-five percent of children with hypoventilation on PSG had echocardiographic evidence of PH. This finding highlights the importance of polysomnographic CO_2 monitoring and calls attention to an area of future research potential. While alveolar hypoxia is thought to be the primary agent of PH, hypercapnia and acidosis are important contributors to this process.[49–52] Previous literature has demonstrated a relationship between pediatric central alveolar hypoventilation syndromes and PH[53–55] but the literature on obstructive hypoventilation and PH in children is limited to older case studies.[34,56–58] In adults, obesity hypoventilation syndrome is associated with an increased risk of PH.[59–62] Diagnosis of obesity hypoventilation syndrome requires demonstration of hypoventilation during wakefulness. None of the patients with hypoventilation on PSG carried a diagnosis of obesity hypoventilation syndrome or respiratory failure, but objective CO_2 assessment was limited to measurements obtained during polysomnography. Thus, we cannot rule out the presence of daytime hypercapnia in these children, although we believe it to be unlikely. Given that all patients had severe OSA, our ability to draw conclusions about the relationship between nocturnal hypoventilation and PH is limited to this group. Further investigation examining the cardiovascular consequences of sleep-related hypoventilation in children with variable OSA severity is warranted.

Children with DS comprised 16.7% of the study population but made up 46.2% of those with PH. Fifty-nine percent of children with DS had a history of CHD and only 15 of 46 children with CHD did not have DS. While the high rate of concomitant CHD in DS made it difficult to ascertain each condition's independent contribution to PH risk among our study cohort, the prevalence of CHD in our group of children with DS is similar to that reported in population-based studies. The observation of an increased rate of PH in children with severe OSA and concomitant DS or CHD, as well as the trend toward an increased prevalence of PH in children with DS and CHD compared with children with DS without CHD, are in concordance with existing knowledge of PH risk in these conditions. DS and CHD are independent risk factors for the development of PH, and the prevalence of PH is increased in patients with DS and CHD compared with individuals with CHD without DS.[63–66] Because our study lacked a comparison group of children without OSA, we cannot solely attribute the finding of PH in children with DS or CHD to the presence of severe OSA. Further research is needed to determine the magnitude by which OSA contributes to PH development in these already-vulnerable patient populations.

Of the 70 children with neuromuscular disease and severe OSA, none had evidence of PH on echocardiogram. Six patients with Duchenne muscular dystrophy had mild to moderate dilated cardiomyopathy. Six other patients with neuromuscular

weakness had hypoventilation on PSG. The absence of PH in this subgroup with multiple risk factors is intriguing. We speculate that patients with neuromuscular weakness may be less capable of generating the very negative intrathoracic pressures needed to increase RV preload and pulmonary blood flow, thereby protecting them from this additional strain on the cardiopulmonary system.

The limitations of this study are largely related to its design. Because our initial cohort was identified by procedure codes for sleep study and echocardiogram, we were unable to determine how many children were diagnosed with severe OSA but did not undergo echocardiogram or compare patients with severe OSA and echocardiogram with those with severe OSA who did not undergo echocardiogram. Twenty-seven percent of children had an echocardiogram prior to PSG. While we suspect that many patients underwent echocardiogram to screen for cardiac abnormalities related to severe OSA, this was not a specific criterion for study inclusion and may have led to selection bias favoring inclusion of children with comorbid conditions such as DS, cardiac disease, and muscular dystrophy. The decision to study only children with severe OSA was based on our institutional practice of referring these patients for echocardiogram. While we considered including children with OAHI < 10 events/h, this methodology would have substantially increased the number of patients who underwent echocardiogram for indications other than OSA. A prospective study whereby all participants undergo PSG and echocardiogram would be useful in further assessing for a relationship between OAHI and PH. PSG and echocardiogram information was recorded from preexisting reports in the electronic health record, and an independent review of raw data to confirm findings or extract missing information was not performed. The primary outcome was based on the presence of echocardiographic findings suggestive of elevated PAP. While echocardiography is a valuable noninvasive screening tool, its findings are largely dependent on the proficiency of the technician, patient cooperation and body habitus, and the interpretation of the reviewing physician. Cardiac catheterization is required to establish a definitive diagnosis of PH. There was significant heterogeneity among diagnoses, which hampered our ability to analyze patients by their respective medical conditions. Children with severe OSA were studied at a single point in time and information on OSA management, response to therapy, and results of subsequent cardiac evaluations was not obtained.

CONCLUSIONS

In conclusion, we found a relatively high prevalence of PH on echocardiogram in a large cohort of children with severe OSA. While this finding lends support to the existing recommendation for PH screening in children with severe OSA, our failure to find an association between OAHI and PH suggests that OSA severity alone may not reliably identify those patients at highest risk. In settings where the availability of echocardiography is limited, we would consider prioritizing screening in children with DS or evidence of nocturnal hypoventilation. Longitudinal research investigating the time frame and circumstances under which PH develops in children with OSA is necessary to optimize timing of initial PH screen and determine conditions under which repeat interval assessment is warranted.

ABBREVIATIONS

ASD, atrial septal defect
BMI, body mass index
CHD, congenital heart disease
DS, Down syndrome
OAHI, obstructive apnea-hypopnea index
OSA, obstructive sleep apnea
PAP, pulmonary artery pressure
$P_{ET}CO_2$, peak end-tidal carbon dioxide
PH, pulmonary hypertension
PSG, polysomnogram
RV, right ventricular
SpO_2, oxygen saturation
TRV, peak tricuspid regurgitation velocity
TST, total sleep time
VSD, ventricular septal defect

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