CHEST

OSA and Cardiovascular Risk in Pediatrics

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OSA occurs in approximately 1% to 5% of children in the United States. Long-term cardiovascular risks associated with OSA in the adult population are well documented. Although changes in BP regulation occur in children with OSA, the pathways leading to chronic cardiovascular risks of OSA in children are less clear. Risk factors associated with cardiovascular disease in adult populations could carry the same future risk for children. It is imperative to determine whether known mechanisms of cardiovascular diseases in adults are like those that lead to pediatric disease. Early pathophysiologic changes may lead to a lifetime burden of cardiovascular disease and early mortality. With this perspective in mind, our review discusses pathways leading to cardiovascular pathology in children with OSA and provides a comprehensive overview of recent research findings related to cardiovascular sequelae in the pediatric population.

CHEST 2019; 156(2):402-413

KEY WORDS: cardiovascular; OSA; pediatrics; risk factors

The prevalence of OSA in children varies with the severity of the disorder.[1] In a population of 5- to 12-year-old children, the prevalence of mild OSA (an obstructive apnea-hypopnea index [OAHI] between one and five events per hour) reaches 25%. The prevalence of moderate OSA (an OAHI $>$ 5 and $<$ 10 events per hour[2]) is approximately 1.2%. Pediatric OSA was first recognized as a serious clinical diagnosis following publication of several case reports describing children with severe pulmonary hypertension and irregular breathing during sleep.[3,4] The improvement in nocturnal breathing patterns and pulmonary hypertension, as well as their cardiopulmonary health, following tracheostomy represented the first link of upper airway obstruction during sleep to cardiopulmonary disease in the pediatric population.[3] Due to the relatively early diagnosis of OSA in children, the clinical presentation, including pulmonary hypertension and cardiac dysfunction, is not routinely encountered in today's practice.

The change in the clinical phenotype of children presenting with OSA to one that lacks an overt manifestation of cardiovascular disease leads to the important question of whether OSA in children still poses a cardiovascular risk. To address this question, the prevalence of known risk factors leading to cardiovascular disease in adults is being evaluated in children with OSA. This approach assumes that risk factors associated with cardiovascular disease in adult populations carry the same

ABBREVIATIONS: AMBP = ambulatory BP; CRP = C-reactive protein; HRV = heart rate variability; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; OAHI = obstructive apnea-hypopnea index; PSG = polysomnography; PTT = pulse transit time

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DOI: https://doi.org/10.1016/j.chest.2019.02.011

future risk for children. However, it is important to recognize that numerous childhood cohorts studied over the last several decades were created to determine the association between cardiovascular risk factors identified during childhood and adult cardiovascular diseases[5,6]; this goal has not yet been completely achieved. One important reason for this delay is the dynamic change in these risk factors over the span of several decades. Specifically, the incidence of cardiovascular disease during adulthood may depend on whether a certain risk factor is sustained from childhood to adulthood or whether it waxes and wanes over time.

Notwithstanding our inability to describe the continuum of cardiovascular health throughout life, there is strong evidence that some cardiovascular risk factors may continue from childhood into adulthood. For example, in a longitudinal study of 493 boys and girls aged 5 to 18 years, elevated systolic BP during childhood was associated with hypertension and metabolic syndrome as adults.[5] It is therefore imperative to determine whether known mechanisms of adult cardiovascular diseases are also important for the development of pediatric disease. With these issues in mind, the present review discusses pathways leading to cardiovascular pathology in children with OSA. Tables 1 through 4 summarize some of the major studies described in this review.[5-24]

BP Dysregulation

As a result of defining BP $\geq$ 95th percentile,[25] the diagnosis of childhood hypertension has been made more frequently over the last several decades.[26,27] Hypertension and BP dysregulation, well-known risk factors for cardiovascular diseases, have been investigated in both cross-sectional and longitudinal studies of children with OSA. Many of these studies examined BP in healthy normotensive children without comorbid conditions. Fewer studies examined the prevalence of OSA in children with hypertension. However, it is important to recognize that the American Academy of Pediatrics revised its definition of pediatric prehypertension in 2017,[25] and the prevalence of prehypertension and/or hypertension in children with OSA may change accordingly. In addition, it is important to note that variability in cardiovascular outcomes in children can be influenced by the age of study participants. Phenotypic changes in preschool-aged children are not as marked as changes in older children, and this factor may be related to the length of time children are exposed to untreated disease.

Prevalence of OSA in Children With Hypertension

The prevalence of OSA in adults with resistant hypertension is as high as 80%, with approximately 50% having moderate to severe OSA.[28] However, there are few data on the prevalence of OSA in children with hypertension. A recent retrospective study[29] that examined 446 children aged 10 to 17 years referred to a hypertension clinic reported a snoring prevalence of 23%. In a subset of children with snoring who underwent polysomnography (PSG), 55% had OSA. Fifty-two percent of children with severe OSA (an apnea-hypopnea index [AHI] $\geq$ 10 events per hour^2) had stage 2 hypertension based on in-office BP measurements.

BP in Normotensive Children

There are several commonly used approaches to study BP control in children with OSA. These include measurements of in-office BP, 24-h ambulatory BP (AMBP) measurements, and pulse transit time (PTT) as a surrogate marker of BP.[7] However, some previous studies also used continuous BP recordings from overnight PSG. In addition to measuring BP during wakefulness and sleep, studies examined BP variability and nocturnal dipping. Marcus et al,[9] for example, first published the results of BP recording during overnight PSG and reported an increase in diastolic BP during both wakefulness and sleep. In children aged 2 to 12 years, systolic and diastolic BPs were associated with the severity of OSA. Additional studies of 24-h AMBP in school-aged and adolescent children showed an increase in diastolic and/or systolic BPs.[10-13] In one study of 24-h AMBP,[10] BP load (defined as the number of measurements exceeding the 95th percentile) was positively correlated with the severity of OSA. Similarly, children with OSA had a higher morning BP surge also associated with the severity of OSA, as measured by using OAHI. In almost all case-control studies that examined BP control, children with OSA had a significantly higher BMI compared with control subjects. As a result, the relative contribution of obesity vs OSA to 24-h AMBP findings was examined. The results revealed that OSA and BMI have similar effects on diurnal systolic BP, diastolic BP, and sleep systolic BP. However, OSA had a significantly greater effect on nocturnal diastolic BP than BMI. Evidence supports the

association between OSA and changes in BP in the pediatric population (Table 1).[7-13]

Because children with OSA have higher BMIs compared with control subjects,[10] and obesity significantly affects the cardiovascular system, some studies were designed to distinguish the effects of OSA vs obesity. In a study of children aged 8 to 18 years, BP and PTT were evaluated in normal weight and obese control subjects and those with OSA. In this study, BMI exhibited combined and independent effects on BP in those with OSA.[8] Other studies have co-varied for BMI,[30-34] all showing that OSA and obesity are independently associated with adverse cardiovascular outcomes. In a 35-year longitudinal study of preadolescent children without OSA, participants who were overweight at the initial visit were significantly more likely to develop OSA in middle age,[6] highlighting the significance of childhood obesity on the development of OSA in adulthood. Although additive effects of obesity and OSA on the cardiovascular system are difficult to distinguish, improvement of cardiovascular sequelae in children with OSA also requires control of obesity.

Nocturnal dipping of BP is an important factor that has a protective effect against cardiovascular disease. In both children and adults, nondipping is defined as a fall in less than 10% of the nocturnal (asleep) BP compared with the daytime (awake) BP. Dipping status, however, can vary depending on the measured BP index.[35] It is well established that a nondipping pattern of diurnal BP variation in adults is an independent predictor of adverse cardiovascular outcomes.[36] In fact, in a meta-analysis of four prospective studies of adults with hypertension, nocturnal BP was a better predictor of cardiovascular outcomes than daytime BP.[37] Several mechanisms have been proposed to explain nondipping of nocturnal BP, including attenuated nocturnal decreases in systemic vascular resistance, increases in sympathetic tone, and decreases in baroreflex sensitivity during sleep.[38,39] In adults with OSA, nondipping BP is well documented and correlates with the severity of the disease.[40-42] Similar observations were made in children with OSA.[14,15] Nondipping nocturnal BP in children 5 to 17 years of age with OSA has been reported in previous studies.[15,16,43] However, in a group of 7- to 13-year-old Australian children with OSA, BP dipping was preserved.[17] Similarly, preserved nocturnal BP dipping is seen in children aged 3 to 5 years with OSA even in the presence of sleep fragmentation.[18] Evidence supports a link between OSA and nondipping BP in children (Table 2).[14-18]

Another parameter of BP control is the variability of diurnal and nocturnal BP. It is evident that the variability of BP between clinic visits and in 24-h AMBP in the adult population carries an increased risk of cardiovascular disease and all-cause mortality.[44,45] Increases in BP variability have also been reported in 5- to 17-year-old children with OSA, and this finding

TABLE 1] Summary of Studies Discussing General Effects of OSA on BP

Study	Year	Study Type	No. of Subjects	Age	What Is Evaluated	Findings
Nisbet et al[7]	2013	Prospective	81 children	3-5 y	PTT	Obstructive events elicit acute cardiovascular changes in preschool-aged children
Horne et al[8]	2018	Prospective	98 children	8-18 y	PTT	BMI has combined and independent effects on BP and heart rate in children with OSA
Marcus et al[9]	1998	Prospective	67 children	2-12 y	BP using arm cuff	Childhood OSA is associated with systemic diastolic hypertension
Amin et al[10]	2008	Prospective	140 children	7-13 y	24-h AMBP	SDB in children associated with increase in morning BP surge, BP load, and 24-h AMBP
Li et al[11]	2008	Prospective	306 children	6-13 y	24-h AMBP	OSA associated with elevated daytime and nocturnal HTN
Leung et al[12]	2006	Prospective	96 children	6-15 y	24-h AMBP	Increased desaturation index is associated with elevation of diastolic BP elevation
Kang et al[13]	2016	Prospective	163 children	4-16 y	24-h AMBP	Prevalence of nocturnal systolic HTN higher in children with OSA

AMBP = ambulatory BP; HTN = hypertension; PTT = pulse transit time; SDB = sleep-disordered breathing.

TABLE 2] Summary of Studies Discussing Nondipping BP in OSA

Study	Year	Study Type	No. of Subjects	Age	What Is Evaluated	Findings
Horne et al[14]	2011	Prospective	105 children	7-13 y	Continuous overnight BP	SDB associated with nondipping BP
Amin et al[15]	2004	Prospective	60 children	7-14 y	Continuous overnight BP	Nocturnal BP dipping was predicted by desaturation index
Xu et al[16]	2013	Prospective	145 children	5-14 y	24-h AMBP	Children with OSA had decreased nocturnal dipping
Horne et al[17]	2013	Prospective	141 children	7-12 y	Continuous overnight BP	SDB does not alter nocturnal BP dipping
Nisbet et al[18]	2014	Prospective	192 children	3-5 y	PTT	Nocturnal dipping is preserved in young children with OSA

See Table 1 legend for expansion of abbreviations.

correlated with the severity of OSA.[15] The role of autonomic dysfunction in BP dysregulation in children with OSA has been explored in several studies. There is now evidence that a broad range of children (from toddlers to teenagers) with OSA have heightened sympathetic tone and decreased baroreceptor sensitivity.[19,20,22,23]

Autonomic balance can also be evaluated by using other measures such as heart rate variability (HRV).[46] Many studies have used HRV to assess sympathetic tone in children with OSA. In a study of children with OSA,[21] autonomic balance, as determined by HRV from overnight PSG, correlated with respiratory disturbance index. In addition, HRV, as a measure of sympathetic activity of the autonomic nervous system, decreased in 2- to 7-year-old children following treatment of OSA with adenotonsillectomy.[47] Morning urinary catecholamine levels also seem to be associated with severity of OSA, indicating that OSA leads to increased sympathetic tone.[19,48] OSA leads to changes in both sympathetic tone and baroreflex sensitivity in the pediatric population (Table 3).[19-23]

Most studies of children with OSA reported increased systolic and diastolic BPs, increased BP variability, and decreased BP dipping. It is important to recognize that not all studies report all three abnormalities in BP. This lack of agreement between studies highlights the fundamental question about the genetic predisposition and gene-environment interactions that lead to a phenotype with increased cardiovascular risk.

The causal relationship between OSA and elevated BP level has been explored through longitudinal follow-up studies of untreated children with OSA and by examining the change in BP following treatment. In a 4-year prospective follow-up study of untreated childhood OSA,[49] baseline OAHI in 9- and 10-year-old children was positively associated with follow-up awake and sleep systolic and diastolic BPs. The change in OAHI was also positively associated with sleep systolic and diastolic BPs. The effect of treatment on BP control has also been reported previously. In multiple cross-sectional studies, treatment with adenotonsillectomy or CPAP was associated with a decrease in BP.[50-56] These studies suggest that a causal relationship between elevated BP and OSA in children might indeed exist. However, these previous observations have not been confirmed through more rigorous randomized controlled trials.

The Rationale for Monitoring BP in Children With OSA

Studies have shown that the BP trajectory from childhood to young adulthood is closely related to end-organ structure and function. In a 23-year longitudinal study of BP in children without OSA recruited between the ages of 5 and 16 years,[24] BP could be successfully tracked into adulthood. The study also showed that the trajectory of systolic BP was a significant predictor of both carotid intimal thickness and left ventricular mass index (Table 4).[5,6,24] Furthermore, studies that examined left ventricular geometry in prehypertensive and hypertensive children between the ages of 5 and 19 years found that both groups had increased left ventricular remodeling and mass compared with normotensive children and that the change in left ventricular geometry increased with increasing BP.[57,58] Left ventricular remodeling and hypertrophy have been described in 5- to 12-year-old children with OSA[59] and were also associated with increasing BP.[10] Although most children are normotensive based on the American Academy of Pediatrics guidelines that precede the 2017 report,[25] observing the BP trajectory of children with OSA is

TABLE 3] Summary of Studies Discussing Changes in Sympathetic Tone and Baroreflex Sensitivity in OSA

Category	Study	Year	Study Type	No. of Subjects	Age	What is Evaluated	Findings
Sympathetic tone	O'Driscoll et al[19]	2011	Prospective	96 children	3-12 y	Overnight urinary catecholamine levels	Overnight urinary noradrenaline (sympathetic tone) related to severity of OSA
	Montesano et al[20]	2010	Prospective	50 children	7-12 y	Ewing test battery	Increase in basal sympathetic activity during wakefulness, dependent on severity of OSA
	Baharav et al[21]	1999	Prospective	20 children	3-14 y	Heart rate fluctuation in PSG	Children with OSA exhibit enhanced sympathetic activity
Baroreflex sensitivity	Chaicharn et al[22]	2009	Prospective	20 children	7-14 y	Baroreflex gain	Vagal modulation remains normal in children with OSA, but baseline sympathetic activity is elevated
	McConnell et al[23]	2009	Prospective	169 children	7-12 y	Baroreflex gain	OSA associated with decrease in nocturnal baroreflex gain and increase in BP variability

PSG = polysomnography.

essential to identifying those at risk for developing clinically significant elevated BP later in life.

OSA and Endothelial Dysfunction

Vascular tone, platelet activity, leukocyte adhesion, and angiogenesis are regulated by the vascular endothelium. Nitric oxide, along with other regulatory factors, is essential to preserving endothelial function. A decrease in nitric oxide bioavailability induces endothelial inflammation that promotes atherosclerosis.[60,61] Therefore, endothelial dysfunction correlates with cardiovascular disease progression and predicts cardiovascular events.[61-64] In children, several studies

TABLE 4] Summary of Several Longitudinal Studies

Study	Year	Study Type	No. of Subjects	Age	What Is Evaluated	Findings
Sun et al[5]	2007	Longitudinal cohort	493 children into adulthood	5-18 y	Standard BP measurements	Children with elevated BP at increased risk of HTN as adults
Bazzano et al[6]	2016	Longitudinal cohort	844 children into adulthood	7-12 y	Anthropometric measurements	Overweight in childhood increases risk for OSA in middle age
Hao et al[24]	2017	Longitudinal cohort	683 children into adulthood	5-16 y	Standard BP measurements, echo	Childhood systolic BP trajectories are associated with subclinical cardiovascular risk

See Table 1 legend for expansion of abbreviation.

described an association between endothelial dysfunction and OSA.[65-68] Treatment of nonobese 6- to 11-year-old children with OSA by using adenotonsillectomy seems to have a beneficial effect on endothelial function in a subset of children with no family history of hypertension.[65]

Inflammation and OSA in Children

The relationship between inflammatory pathways and OSA is complex and likely to be bidirectional. There are multiple facets to the inflammatory response in the context of OSA. Evidence exists of systemic inflammation that is quantified by circulating cytokines, acute-phase reactants, and inflammatory cells. Evidence also exists of tissue- or organ-specific inflammation that mediates some of the phenotypic characteristics observed in children with OSA. Lastly, there is a potential role of inflammation in the development of OSA (Fig 1).

Systemic Inflammation

Multiple studies have reported increased levels of plasma cytokines in children with OSA across many age groups.[69-75] However, fewer studies have examined the relationship between circulating cytokines and cardiovascular end points. In children with OSA, circulating cytokines and/or inflammatory cells were found to correlate with the degree of endothelial dysfunction and PTT.[66,74,76] Parallel to the increase in proinflammatory cytokines is an increase in acute-phase reactants,[77-79] such as C-reactive protein (CRP), and adipokines.[74,80] Although the role of acute-phase

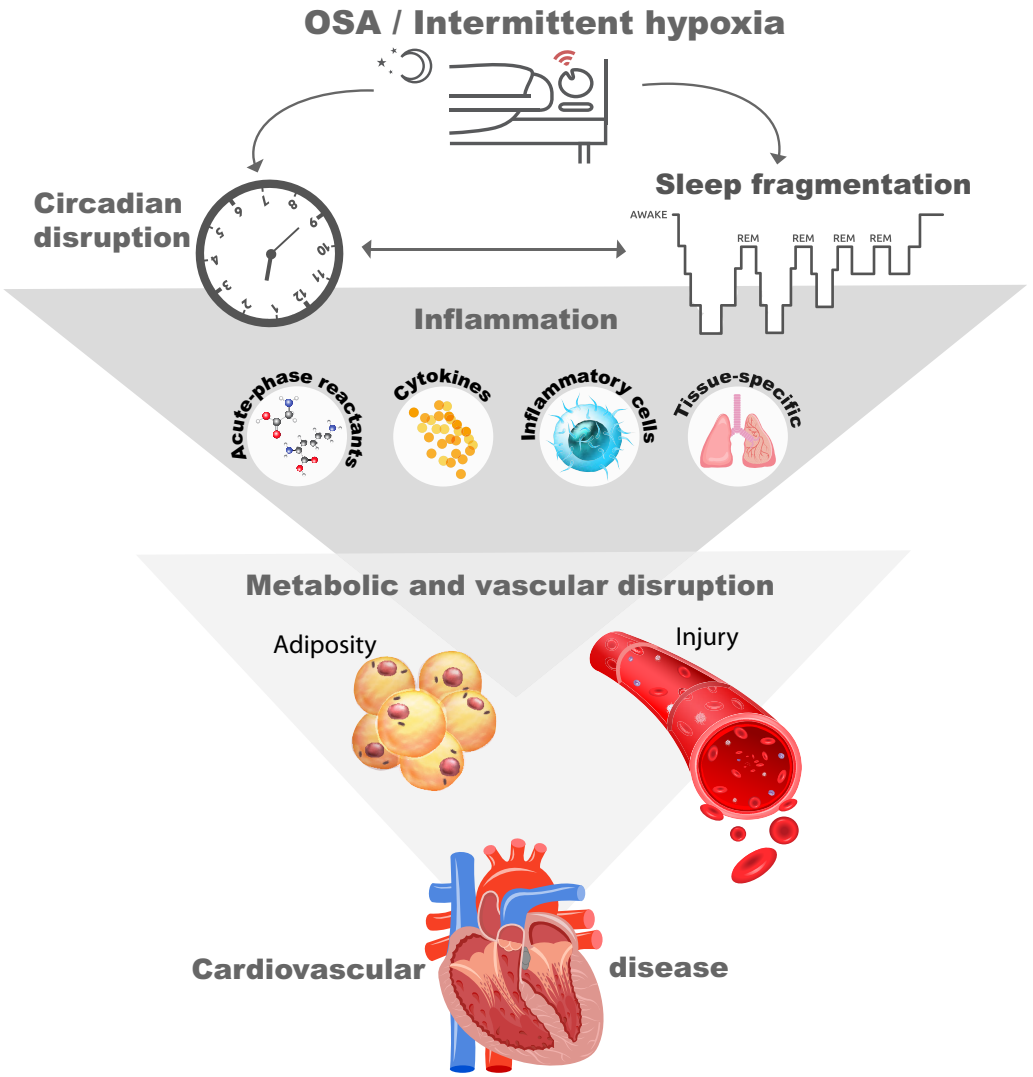

Figure 1 – *Relationship between inflammation and OSA. Systemic and tissue-specific inflammation mediates cardiovascular and metabolic disturbances that also contribute to the relationship between central adiposity and OSA. REM = rapid eye movement.*

reactants in mediating and or protecting from cardiovascular injury needs further investigation, some evidence suggests that acute-phase reactants such as CRP may play dual roles: one as proinflammatory in the process of endothelial injury, and the second to protect from the proinflammatory effects of circulating cytokines.[74]

Tissue Inflammation in OSA

Preclinical studies show that intermittent hypoxia induces endothelial inflammation and dysfunction through upregulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor that upregulates > 200 genes.[81-85] The pathways mediating endothelial inflammation and injury observed in preclinical studies have been tested in children with OSA. These studies show that the same inflammatory pathways were closely associated with endothelial dysfunction.[67,86]

Adenoid and tonsillar tissue from children with OSA have characteristic distributions of lymphocyte subsets.[87] There is also high expression of leukotrienes and their receptors in the adenotonsillar tissues,[87-89] which elicit a cellular proliferation of tonsillar tissue. Demain and Goetz[90] showed that long-term use of nasal corticosteroids in 5- to 11-year-old children could reduce the size of adenoid tissue and treat isolated nasal airway obstruction. A similar treatment regimen showed a significant decrease in obstructive respiratory events in children aged 1 to 10 years with OSA.[91] Several prospective clinical studies have also reported a therapeutic role for leukotriene modifiers in pediatric OSA.[92,93] These data suggest that the inflammatory response observed in children with OSA may also contribute to further airway obstruction by inducing hypertrophy of tonsillar and adenoid tissue.

Contribution of Inflammation to OSA

The strong association between obesity and OSA in children and adults has been repeatedly reported in multiple studies that have examined the risk factors for OSA, with central obesity playing an important role in mediating this relationship. Several explanations for the potential causal association between obesity and OSA have also been proposed. Data suggest that the association between central adiposity and OSA is mediated through an inflammatory process.[80] In this longitudinal study examining the change in obesity, OSA, and inflammatory biomarkers from early childhood to adolescence, changes in CRP were closely associated with changes in waist circumference and follow-up OAHI. These results suggest that inflammation may explain the association between increasing central obesity and OSA severity. Additional studies reported that genetic polymorphisms of IL-6, tumor necrosis factor α, and CRP contribute to OSA.[74,94-97] Based on these observations, it is plausible that obesity-related inflammation represents one mechanism of OSA in overweight and obese children.

Insulin Resistance and Glucose Homeostasis in Pediatric OSA

It is plausible that even in the absence of obesity, OSA may increase the risk for cardiovascular disease by inducing insulin resistance. Insulin resistance is directly associated with an increased risk for atherosclerosis.[98] Artificially induced sleep fragmentation is associated with decreased morning insulin sensitivity,[99] and the degree of sleep disruption is correlated with the level of insulin resistance.[100] Intermittent hypoxia-induced inflammation led to insulin resistance in a murine model of OSA.[101] Intermittent hypoxia also induces arousal in mice.[102] Furthermore, intermittent hypoxia in healthy adults decreases insulin sensitivity.[103] In a large pediatric cohort of normal and overweight children aged 5 to 12 years, sleep fragmentation was independently and positively associated with insulin resistance measures.[104] Although obesity is also associated with insulin resistance, complicating causal relationships between OSA, obesity, and cardiovascular disease, it is apparent that sleep fragmentation associated with OSA may play a role in disrupted homeostasis commonly seen in children with OSA.

Circadian Misalignment in Pediatric OSA

Advances in research on control of the circadian clock have expanded our understanding of the impact of circadian misalignment on human disease.[105] Variations of the endogenous circadian rhythm or misalignment between the clock and environmental time cues negatively affect the sleep-wake cycle and can lead to cardiovascular disease.[106,107] Humans have developed an endogenous clock that follows the light-dark cycle.[108] This system is hierarchically organized[109,110] and is composed of the central clock, located in the hypothalamus,[111] and peripheral clocks throughout the body that contain autonomous oscillators.[112-114] This feedback loop comprises activators and repressors that orchestrate transcription for thousands of genes in all cells over the 24-h rhythm.[109,115]

Virtually all cardiovascular and metabolic functions have a daily rhythm that is regulated by clock genes. Diurnal changes in BP and heart rate, cardiac remodeling, and contractility follow a diurnal rhythm.[116] Furthermore, glucose homeostasis is dependent on alignment of the circadian rhythm of multiple organs.[117-119] Sleep fragmentation in adolescents with sleep disorders led to clock gene dysregulation and decreased glucose tolerance, showing the role of circadian rhythm disturbances in carbohydrate metabolic dysfunction.[120] Cytokines that mediate cardiovascular end-organ damage also follow a diurnal rhythm.[121-123] Given the number of cardiac, metabolic, and immunologic functions that exhibit circadian rhythmicity, it is possible that circadian misalignment is closely affiliated with other mechanisms which are associated with cardiovascular disease in children with OSA.

Preclinical studies reported increased left ventricular end-systolic and end-diastolic dimensions and reduced cardiac contractility in circadian rhythm-disturbed animals.[124,125] In humans, the impact of circadian misalignment on the cardiovascular system has been largely investigated in adult shift workers.[126] Sleep restriction and circadian misalignment in adults are associated with increased CRP levels and insulin resistance,[127] decreases in cortisol levels and changes in proinflammatory and antiinflammatory cytokines,[128] and increases in 24-h systolic and diastolic BPs.[129] There is limited evidence of circadian misalignment in adults and children with OSA. One study in adults showed that OSA has a significant effect on peak serum melatonin levels and that 3-month CPAP use restores the physiologic rhythm of melatonin secretion.[130] In a large prospective study of > 13,000 adults, shortened sleep duration and OSA were independently associated with major coronary events.[131] Interestingly, OSA had an additive effect to short sleep and shift work hours on the risk of cardiovascular disease.

Evidence regarding the risks of circadian misalignment that accompany OSA has been identified from the change in the diurnal rhythm of mediators of inflammation and immunity. It has been suggested that phases of rest vs activity influence the balance between proinflammatory and antiinflammatory mediators.[132] The active phase favors an antiinflammatory state, whereas rest favors a proinflammatory state. Although there are no data from adult OSA populations regarding changes in the diurnal rhythm of inflammatory mediators, a preliminary study in children showed changes in cytokine rhythmicity because of OSA.[74] In healthy control subjects, tumor necrosis factor α, IL-6, and IL-8 levels were higher in the evening (Fig 2). However, children 6 to 13 years old with OSA exhibited higher levels in the morning. This reversal of diurnal rhythmicity occurred in addition to overall higher cytokine levels in children with OSA compared with control subjects. Although these data are derived from one single cross-sectional study, the results may suggest that the loss of a normal diurnal rhythm of

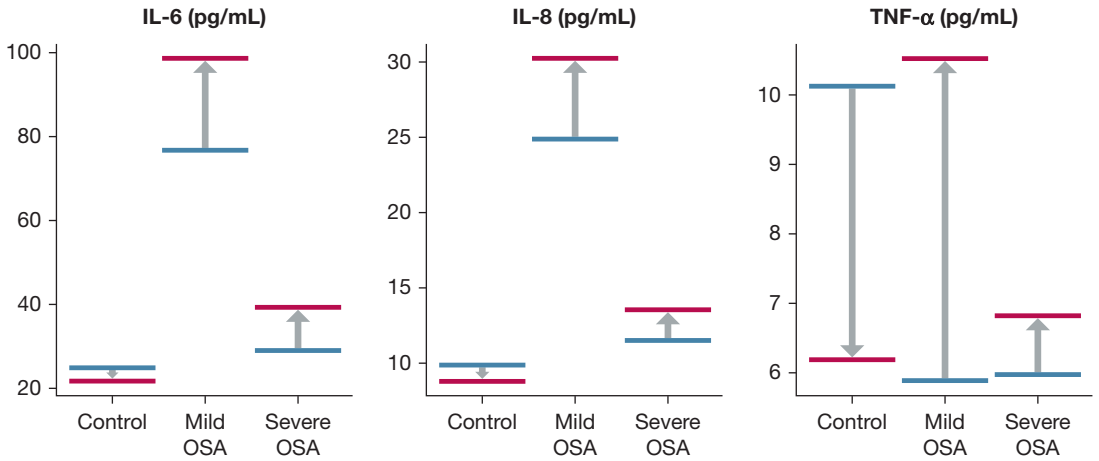

Figure 2 – *Cytokine levels (evening [blue lines] vs morning [red lines]) for healthy participants and children with mild vs severe OSA; data are reported as mean ± SD. Healthy participants and children with OSA aged 5 to 13 years were recruited to the study. All participants underwent overnight polysomnography with evening and morning blood draws for cytokine and acute-phase reactant level measurements. Cytokine levels were measured at 6:00 PM and 6:00 AM. Serum IL-6, IL-8, and TNF-α exhibited a difference in diurnal variation in children with OSA compared with healthy control subjects. In control patients, cytokine levels decreased from evening to morning. In children with mild and severe OSA, cytokine levels increased from evening to morning. TNF-α = tumor necrosis factor α. The figure was created by using data presented previously by Smith et al.*[74]

inflammation in OSA could be a mechanism of sustained inflammatory response throughout a 24-h period.

The effects of OSA on the circadian rhythm of hormone levels could be associated with pathophysiologic consequences seen with untreated disease. Nocturnal awakenings seen in OSA lead to alterations in the hypothalamic-pituitary-adrenal axis and increased pulsatile cortisol release.[133] As the major product of the hypothalamic-pituitary-adrenal axis, cortisol plays a significant role in metabolic and BP regulation.[134] Although previous large-scale studies have not identified a difference in cortisol levels in patients with OSA, demonstration of changes in rhythmicity would require careful and repeatedly timed measurements.[135] Recent research in mice has shown that flattening of daily glucocorticoid oscillations (as seen in chronic conditions that alter glucocorticoid secretion) results in increases in fat mass and weight gain.[136] It is possible that changes in hormone rhythmicity in the presence of OSA could be linked to weight gain.

Future Directions

As the prevalence of OSA increases in the pediatric population, the long-term socioeconomic impact and burden for patients, families, and the medical community will only worsen. Much research is now focused on identification of the novel mechanistic pathways that lead to pathophysiologic progression of untreated disease. For example, evaluation of microRNA profiles and transcriptome profiling in patients with OSA have uncovered potential target genes for future medical intervention.[137-141] Identification of other upstream pathways, such as those that regulate the circadian clock, may lead to the development of new diagnostic techniques and medical therapies.[142]

Conclusions

Published literature supports the hypothesis that children with OSA have cardiovascular and inflammatory processes such as those associated with cardiovascular disease in adults. Further research is needed to determine the causal relationship between OSA and the presence of cardiovascular risk factors as well as the reversibility of these processes with adequate treatment. Furthermore, there is a gap in knowledge pertaining to factors that determine whether these processes that begin during childhood translate into cardiovascular diseases during adulthood.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

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