COMMENTARY

From Obstructive Sleep Apnea in Childhood to Cardiovascular Disease in Adulthood: What is the Evidence?

Commentary on Montesano et al. Autonomic cardiovascular tests in children with obstructive sleep apnea syndrome. SLEEP 2010;33:1349-1355.

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IN THIS ISSUE OF *SLEEP*, MONTESANO AND COLLEAGUES HAVE EMPLOYED A BATTERY OF CARDIOVASCULAR TESTS AIMING TO INVESTIGATE autonomic nervous system activity during wakefulness in children with obstructive sleep apnea (OSA).[1] In agreement with findings in adults,[2] the investigators established diurnal sympathetic-to-parasympathetic imbalance in sleep apneic children when compared to control subjects. To interpret their findings, the authors comment that augmented sympathetic activity has been implicated in the pathogenesis of increased cardiovascular morbidity in adults with OSA. Furthermore, the authors suggest that clinical significance of the reported autonomic changes in children with sleep apnea remains to be elucidated.[1]

OSA has not been Commonly Associated with Overt Cardiovascular Disease in Childhood

Patency of the upper airway during sleep in children is maintained by complex interactions between upper airway resistance, pharyngeal collapsibility, pharyngeal dilator muscle tone, and negative intrapharyngeal pressure generated by the inspiratory muscles. This fine balance of mechanical forces may be disrupted by one or more abnormalities (adenotonsillar hypertrophy, obesity, craniofacial anomalies, abnormal neuromotor tone) resulting in OSA, a syndrome of functional impairment of the upper airway during sleep. Intermittent upper airway obstruction during sleep and the associated blood gas exchange abnormalities, arousals from sleep and negative intrathoracic pressure swings may ultimately lead to complications.

Similar to what has been reported in adults with sleep apnea, data collected from the general population have confirmed that obstructive sleep disordered breathing in children is related to increased prevalence of central nervous system morbidity including excessive daytime sleepiness and poor academic performance.[3] Nonetheless, limited evidence supports a relationship of sleep apnea in childhood with overt short-term or long-term cardiovascular disease. This is in contrast to the increased frequency of coronary heart disease, heart failure, and stroke reported in adults with OSA.

Submitted for publication August, 2010
Accepted for publication August, 2010
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In the pediatric literature, there are case reports of cor pulmonale related to severe upper airway obstruction and a few population-based studies indicating positive correlation of OSA severity and blood pressure levels or risk for hypertension.[4] Most other pediatric investigations have not revealed OSA-associated symptomatic cardiovascular disease, but rather activation of pathogenetic mechanisms that could lead to cardiovascular morbidity, provided that sleep disordered breathing persists for a long time. More specifically, maladaptive responses to sleep apnea have been recognized in affected children, such as sympathetic nervous system activation, increased oxidative stress, systemic inflammation, endothelial dysfunction, reduced nocturnal baroreflex gain and subclinical abnormalities in cardiac structure and function detectable only by echocardiography.[5-7]

Sympathetic Overflow has been Found Consistently in Pediatric OSA

Intermittent hypoxemia and arousals from sleep accompanying OSA may induce sympathetic overflow.[2] Sympathetic nervous system activity can be measured either directly by recording muscle sympathetic nerve output (peroneal microneurography)[2] or indirectly by analyzing heart rate variability,[8,9] using peripheral arterial tonometry,[10] or quantifying urinary excretion of catecholamines.[11]

Upon termination of an obstructive event, R-R interval in the electrocardiogram (ECG) becomes shorter (faster heart rate) compared to the pre-event period and the immediate post-event R-R interval variability diminishes.[8] Periods of sleep free of abnormal respiratory events are characterized by reduced mean R-R interval and R-R interval variability, as well.[9] Decreased heart rate variability during sleep and increased urinary excretion of catecholamines are indicative of enhanced sympathetic activity in children with OSA.[11]

In this issue of *SLEEP*, Montesano et al. supply additional evidence for the presence of sympathetic overactivity in pediatric OSA by evaluating sleep apneic subjects during wakefulness.[1] The investigators subjected children with and without sleep apnea to cardiovascular challenges that can elicit autonomic responses. The applied battery of cardiovascular challenges included the head-up tilt test, the Valsalva maneuver, and the deep breathing test. Changes in heart rate, R-R interval, and blood pressure were the outcome measures selected for quantification of sympathovagal balance. The investigators have made evident that subjects with OSA have augmented sympathetic tone and possibly reduced parasympathetic activity relative to

children without sleep apnea. However, it should be noted that OSA severity did not predict autonomic responses consistently. It also remains unknown whether the detected sympathovagal imbalance can be corrected by successful treatment of OSA.

In another study, O'Brien and Gozal[10] employed analogous challenges in order to elicit sympathetic responses during wakefulness, namely vital capacity sighs and hand immersion in ice-cold water. Peripheral arterial tonometry was applied to monitor the pulsatile volume changes of the finger, with sympathetic vasoconstriction resulting in attenuation of the monitored signal. Exaggerated sympathetic responses were found in the group with sleep apnea.

It is now clear in the literature that sympathetic overactivity in adult life has multiple detrimental effects on the cardiovascular system. Among other adverse consequences, it contributes to the pathogenesis of hypertension, development of hypertension-related end organ damage, and deterioration of heart failure.[12]

Can Pediatric OSA lead to Cardiovascular Disease in the Long Term?

Recent data from the TuCASA longitudinal study have shed some light on the natural history of pediatric OSA.[13] When a cohort of children with initial ages 6 to 12 years was re-evaluated approximately 5 years later (ages 10 to 18 years), OSA had resolved in 70.8% of the initially diagnosed cases. During the same 5-year period, a 63.8% reduction in the frequency of excessive daytime sleepiness (central nervous system morbidity) was demonstrated. Male gender and increasing body mass index percentile were significant predictors of OSA in adolescence.

It is conceivable that as children grow older and adenotonsillar tissue becomes smaller in size, the frequency of OSA decreases, with the exception of subjects who become overweight or obese. Obesity predisposes to dysfunction of the upper airway during sleep and OSA in overweight and obese children and adolescents increases their risk for having metabolic syndrome.[14] Hence, there may be a bi-directional association between obesity and OSA (obesity, more severe OSA, more severe obesity) with inflammation, sympathetic activation, and insulin resistance being the intermediaries that promote atherosclerosis and cardiovascular disease.[15] Inclusion of cardiovascular health outcomes in ongoing and future population-based pediatric cohorts will clarify the potential etiologic relation of pediatric OSA and cardiovascular disease in adulthood.

DISCLSOURE STATEMENT

Dr. Kaditis has indicated no financial conflicts of interest.

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