than PaCO₂ measurements, and short-term changes in CO₂ do not reflect long-term adaptation.

Such nuances, however, engender more questions. Although the study by Wijesinghe and colleagues involved 100% oxygen supplementation, what, if any, is the impact of commonly used lower concentrations of supplemental oxygen on the control of breathing during wakefulness? Does low-flow oxygen during sleep, with or without NPPV, affect CO₂ retention? Is the degree of CO₂ retention exaggerated in states of acute-on-chronic hypercapnic respiratory failure related to OHS? What factors underlie the interindividual differences seen in CO₂ retention? Undoubtedly, further research is needed in the field. In the meantime, clinicians should be judicious with oxygen supplementation when treating patients with obesity and hypoxemia, whereas researchers need to determine whether oxygen supplementation in the absence of NPPV therapy is helpful or harmful in this patient population. Finally, because hypoxemia during wakefulness and during sleep improves in many patients after a few weeks of adequate therapy with NPPV,⁶ clinicians should monitor oxygen saturation in patients with OHS after NPPV initiation and probably discontinue oxygen as early as possible.

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Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Mokhlesi has received consultant fees from Philips/Respironics. Drs Tulaimat and Parthasarathy have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.10-2858

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Pediatric Sleep Apnea

The Brain-Heart Connection

Over the past several decades, it has become apparent that obstructive sleep apnea (OSA) significantly elevates the risk of cardiovascular disease and associated mortality, particularly in adults.¹ However, the causal relationships between OSA and cardiovascular disease have been difficult to extricate because of the confounding effects of frequently

overlapping and associated conditions, such as obesity, cigarette smoking, and age. Examination of the physiologic consequences of OSA in children is obviously less likely to be contaminated by several of these confounding variables. Conversely, it was assumed that the strength of the cardiovascular signal caused by OSA would be remarkably smaller or potentially absent altogether, thereby hampering the potential signal-to-noise ratio and, as such, precluding any valid insights into the OSA-induced downstream cardiovascular alterations.

In a series of studies spanning the past decade, the cumulative evidence has dispelled the previously formulated assumptions and shown that OSA in children can indeed lead to cardiovascular dysfunction.² Thus, the maladaptive responses induced by OSA can affect cardiovascular functions despite the a priori underlying presence of a normal cardiovascular system, as is typical of childhood. It is reasonable to speculate that the combination of large swings in intrathoracic pressures elicited by obstructed breathing efforts with recurrent arousals and resultant sleep fragmentation as well as with intermittent hypoxic and hypercapnic gas exchange abnormalities are all likely to contribute to the development of cardiovascular disease.² Although the mechanisms linking OSA to secondary systemic hypertension and left ventricular dysfunction in children remain incompletely delineated,³ maladaptive autonomic nervous system tonic and reflective responses, disruption of endothelial homeostasis, and systemic inflammation all could lead to increased systemic vascular resistance, accelerated atherogenesis, and disruption of dynamic vasomotor control.

In this issue of *CHEST* (see page 1050), Muzumdar and colleagues⁴ report on their assessment of the characteristics of autonomic nervous tone in 18 children with OSA as derived from heart rate and heart rate variability (HRV) analyses. The children studied were young and, therefore, unaffected by potential changes imposed by puberty. Although the effect of obesity was controlled by relatively well-matched BMI *z* scores, it is noteworthy that BMI *z* scores were 1.34 in the OSA group and 1.29 in the control group.⁴ These BMI *z* scores are equivalent to the 90th percentile, implying that a large proportion of the children in this study were at least overweight, if not overtly obese.

Increases in sympathetic tone in pediatric OSA have been described previously through assessments of HRV,^{5,6} pulse rate variability using pulse oximetry,⁷ and pulse arterial tonometry.⁸ The main novelty of this study is the examination of HRV in the same children following adenotonsillectomy (AT), the usual first line of treatment in children with OSA.⁹ In their series, Muzumdar et al⁴ showed that AT was accompanied by significant reductions both in heart rate and

in the ratio of low-frequency to high-frequency band power (LF/HF), a marker of sympathetic tone, suggesting and confirming the previously reported presence of increased sympathetic activity in pediatric OSA.^{10,11} Furthermore, the LF/HFs in children with OSA were reduced to control levels following AT, indicating that the autonomic derangements ascribed to pediatric OSA are effectively reversed by treatment.

Although endothelial dysfunction in children with OSA also improves following AT,¹² it is important to note that AT is much less effective at eradicating OSA than previously anticipated, particularly in the context of concurrent obesity.^{13,14} In fact, six (33%) of the 18 children in the present cohort had evidence of residual OSA post-AT of moderate severity, and OSA was only effectively cured with AT in two (11%) of the 18 children.⁴ Thus, even partial improvements in the severity of OSA yield returns of altered LF/HF to within normal levels. Stratification to post-AT apnea-hypopnea index (AHI) > 5/h and post-AT AHI > 5/h groups further revealed significant reductions in LF/HF in stages N3 and rapid-eye-movement sleep in children with post-AT AHI < 5/h but absence of any significant changes in LF/HF when post-AT AHI remained > 5/h. These findings support the notion that a threshold for the magnitude of respiratory disturbance may be present in children and that such a threshold likely revolves around an AHI of 5/h, whereby the tonic sympathetic activation elicited by the presence of OSA appears to be manifest only after a particular level of disease severity is reached. Before seeking reassurance in such deductions, however, we also should point out that elevations in systemic BP may occur in children with primary snoring¹⁵ (ie, in the presence of AHI < 1/h). Therefore, the normalization of LF/HFs reported by Muzumdar and colleagues⁴ may be inherent to the small size of the cohort in the study, which does not allow for ruling out the presence of a β error.

Another interesting finding was that the children with OSA and obesity had considerably higher LF/HF ratios than the nonobese children with OSA.⁴ However, AT resulted in rather robust reductions in LF/HF in the children with OSA and obesity to levels very similar to the nonobese children. Although the proportion of children with residual OSA in the obese and nonobese cohorts is not stated, the findings suggest that AT effectively reduces LF/HF and, hence, sympathetic predominance in children with obesity, a condition that has been intrinsically associated with elevated sympathetic activity.^{16,17}

Taken together, the findings by Muzumdar and colleagues support the notion that OSA in children is associated with elevated sympathetic reactivity as derived from HRV measures and that such alterations are potentially reversible with effective treatment.

Thus, persistent autonomic dysfunction that ultimately leads to cardiovascular disease may originate during childhood, particularly in children who develop OSA and either remain undiagnosed or are treated late.

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Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Funding/Support: Dr Gozal is supported by the National Institutes of Health [Grant HL-65270].

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DOI: 10.1378/chest.10-2803

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