Beyond the Retrotrapezoid Nucleus in Congenital Central Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS) is a rare disorder presenting with ventilatory dysfunction primarily during sleep that is caused by variants in the PHOX2B (paired-like homeobox 2B) gene with the majority of patients having polyalanine repeat expansion mutations. About 10% of patients with CCHS have non–polyalanine repeat expansion mutations that are usually associated with more severe phenotypes where the majority of the patients require ventilatory support during wakefulness and sleep. The retrotrapezoid nucleus (RTN) includes a well-defined subset of carbon dioxide–sensitive neurons characterized by the expression of Phox2b gene. Genetic depletion of RTN neurons by expression of a Phox2b mutation causes hypoventilation and near absence of the hypercapnic ventilatory response. The RTN regulates several aspects of the breathing cycle, including inspiratory and expiratory activities, which vary across the different stages of consciousness and sleep. As a result, the components that determine $\dot{V}_E$ (respiratory frequency and inspiratory amplitude) exhibit large variation depending on the state of consciousness and stages of sleep. The hypoventilation and the variation in the components of $\dot{V}_E$ in CCHS, in turn, may impact the ability of the autonomic system to maintain body homeostasis that results from the close interactions between the respiratory system and the sympathetic and parasympathetic systems. These impaired autonomic features include control of blood pressure, temperature, and glucose. The autonomic nervous system is also inherently dysregulated in individuals with CCHS, which may influence the central respiratory control and worsen the degree of hypoventilation in CCHS. To date, strong emphasis has been placed on the consequences of the autonomic dysregulation of the cardiovascular system. However, there is limited understanding of how the brain of individuals with CCHS is impacted by the collective effect of the genetic mutations, hypoxia, hypercapnia, and autonomic dysregulation. In this issue of the *Journal*, Vu and colleagues (pp. 340–349) provide novel and unique data on the regulation of cerebral blood flow in response to head-up tilt testing (HUT) (1). Specifically, the authors examined the cerebral autoregulation during orthostatic challenge. There are strong reasons to unravel potential mechanisms of disturbed cerebral perfusion. First, there is strong evidence that brain injury in individuals with CCHS extends beyond the retrotrapezoid nucleus and adjacent brain stem regions. Structural and functional changes of the insular, frontal, and cingulate cortices, cerebellum, basal ganglia, mammillary bodies, and hippocampus have been demonstrated (2–5). Whether these more generalized injuries represent consequences of *PHOX2B* on the development and differentiation of the network of autonomic neurons or are secondary to the autonomic deficit needs to be investigated. The study by Vu and colleagues sets the stage to explore these important questions. Furthermore, studies that followed individuals with CCHS over several years indicate that brain injury progresses with advancing age (6). Genetic programing driven by variants of PHOX2B transcription factor in contrast to the secondary insult from hypoxia and hypercarbia and autonomic dysregulation also deserve further research.

Second, although sufficient evidence is still weak, there are several published reports suggesting that some neurocognitive functions in individuals with CCHS are lower than the general norm (7–9).

To shed light on the origins of brain injury and impaired neurocognitive outcomes in individuals with CCHS, Vu and colleagues examined one aspect of cerebrovascular reactivity that involves vascular tone changes in response to fluctuations in arterial blood pressure. Cerebrovascular reactivity is the ability of vascular smooth muscle to change basal tone in response to variations of physiologic parameters, such as arterial blood pressure, and metabolic factors, such as cerebral carbon dioxide and oxygen levels (10). When cerebrovascular reactivity is exhausted, cerebral blood flow becomes dependent on systemic arterial blood pressure. Hence, there is a positive correlation between surrogate measure of cerebral blood flow (cerebral oximetry index) and mean arterial blood pressure. In Vu's study, cerebral autoregulation at rest in individuals with CCHS did not differ from that in normal control subjects. However, during orthostatic stress, a positive correlation between mean arterial blood pressure and cerebral blood flow emerged in individuals with CCHS. The clinical importance of this observation is that the large swings of blood pressure in individuals with CCHS may push the limit of the physiologic parameters to effectively regulate vascular smooth muscle tone and, therefore, cerebral blood flow depends essentially on blood pressure–driven mechanisms. Under these conditions, extremes of low or high blood pressure may lead to transient hypo- or hyperperfusion of the brain, respectively. Differences in cerebral autoregulation during orthostatic testing between individuals with CCHS and normal control subjects have to be discussed in the context of blood pressure response to HUT in the two groups as the authors attempted to do. Not surprisingly, individuals with CCHS exhibited a larger drop in blood pressure during HUT than control subjects. This is explained by the known deficit in sympathetic and parasympathetic baroreflex in CCHS. The control group did not have the same magnitude of blood pressure drop and therefore had shorter time with elevated cerebral oximetry index. The overall conclusion from the data presented in this study is that the disturbed cerebral autoregulation in CCHS is due to autonomic failure of blood pressure control and not to inherent failure of other mechanisms that regulate cerebral blood flow. Recognizing that this study examined only one aspect of autoregulation, specific studies of other mechanisms of cerebral reactivity may provide different conclusions in the future. An

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important limitation of this study that the authors had little control over is the heterogeneity of the study population. Fifty-four percent of subjects had diaphragm pacing, 81% had a tracheostomy, and 48% were mechanically ventilated during HUT testing. It is likely that the interactions between breathing and the autonomic control of the cardiovascular system in individuals who are breathing spontaneously differ from those requiring ventilatory assistance. A standardized clinical management of individuals with CCHS and data collection across centers may be the only approach to overcome the limitations imposed by retrospective single-center studies. ■

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Tuberculosis: First in Flight

The ongoing coronavirus disease (COVID-19) pandemic has focused global attention on the airborne spread of infection, but tuberculosis (TB) was the first disease in which airborne transmission was convincingly demonstrated after many decades of doubt. The first line of solid evidence was presented in a series of studies documenting remote transmission from humans to guinea pigs (1), followed by reports of human-to-human airborne transmission in closed environments, such as ships (2). More recently, household contact studies have provided valuable evidence regarding transmission dynamics (3–5). Nevertheless, there is now substantial evidence that most transmission occurs outside the household (6, 7).

South Africa faces a devastating TB epidemic that is driven by widespread community transmission of *Mycobacterium tuberculosis*. A recent national survey found a prevalence of 852 cases per 100,000 individuals (8). The annual risk of infection is highest among adolescents and young adults, who often travel and have extensive social networks with multifamily households (9, 10). Schools may represent venues of amplified *M. tuberculosis* transmission (11) and, if so, would provide a logical intervention point for mass screening.

In this issue of the *Journal*, Bunyasi and colleagues (pp. 350–356) provide a detailed look at school environments in Worcester, South Africa, combining novel genomic DNA sampling with ambient carbon dioxide (CO_2) concentration measurements (as a marker of ventilation) and TB symptom screening (12). High-volume air filtration was performed for a median of 40 minutes in 72 classrooms and assayed by droplet digital PCR (ddPCR) for *M. tuberculosis* DNA. Positive DNA samples were found in 18% and 10% of samples in classrooms and clinics, respectively.

The documentation of airborne *M. tuberculosis* in classrooms from this study is an important advance, especially considering the brief period of air sampling. However, the value of estimating an average risk of an occupant inhaling one *M. tuberculosis* DNA copy as an outcome measure is unclear. We know of no data suggesting that the inhalation of one *M. tuberculosis* DNA copy equates to a transmission event or that the process of acquiring

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