Associations between Parasympathetic Activity in the Month after Birth and Wheeze at Age 2–3 Years

To the Editor:

Increased parasympathetic activity (PSA) has been implicated in airway hyperreactivity and asthma morbidity (1–3). In a prospective birth cohort study, we previously observed that rhinitis and watery eye symptoms in infancy, which in older children and adults can result from increased PSA, predicted future exercise-induced wheeze at school age; however, objective measures of PSA were not made in that study (4). In newborns and infants, PSA assessments can be made during sleep by heart rate (HR) and high-frequency HR variability (HF-HRV) measurements in the resting or basal state, and by responses to a head-up tilt challenge, which provokes vagal withdrawal and activation (5, 6). Measures of HRV differ as a function of sleep state (7). Infant sleep states (active/REM or quiet) can be classified based on respiratory rate variability with the use of a recently developed algorithm (8). Using a prospective birth cohort study, we tested the hypothesis that increased basal HF-HRV and responses to tilt in HR and HF-HRV assessed in the first month of life would be associated with report of wheeze at age 2–3 years.

Children living in South Dakota were enrolled in the Safe Passage Study, which was designed to investigate prenatal risks for sudden infant death syndrome and stillbirth (9). Cardiorespiratory function was evaluated for newborns (12–96 h after birth) and/or at age 1 month. PSA was summarized using three measures of HR and HRV for these analyses (methods described in Reference 6). Briefly, basal HF-HRV was defined as the variation in HR within the normal range of infant breathing rates using spectral analyses during a 10-minute baseline period. An acute change in HR to a 45° head-up tilt test was defined as the maximum minus the minimum HR recorded during the first 15 seconds after reaching the head-up position (median of up to three tilts). A sustained HRV response to head-up tilt was defined as the median value during the 30-second period immediately before each tilt subtracted from the median value during the last minute in the head-up position (~45 s after reaching the head-up position). Results were analyzed for both active sleep (AS) and quiet sleep (QS) epochs, although not all infants had epochs of both states. Newborn data were used when valid measures were available for both newborns and 1-month-old infants. Parents of a subset of participants ($n = 312$) answered the following question when their child was 2–3 years old: "In the past year, has your child had wheezing or whistling in the chest?" Generalized estimating equations were used to calculate the relative risk (RR) of wheeze at age 2–3 for an interquartile range increase in HRV measures, controlling for potential confounders and covariates.

Of the 312 children, 22% had a report of wheeze at age 2–3 years. Wheeze was more common among boys than among girls (29% vs. 16%; $P = 0.005$). There was no significant difference in wheeze by race or exposure to prenatal alcohol or tobacco smoke (all $P > 0.3$).

Among the 312 infants, HRV measures were available for AS and QS in $n = 282$ and $n = 139$ children, respectively. HR and HRV responses to tilt were available for AS and QS in $n = 254$ and $n = 178$ children, respectively. The prevalence of wheeze at age 2–3 years did not differ significantly ($P > 0.05$) among children with data for AS and QS.

There were no associations between any of the HRV measures for AS and wheeze at age 2–3 years (Table 1). In a model adjusting for sex, gestational age, fetal alcohol and tobacco exposure, and study location, PSA-mediated changes in acute HR and sustained HRV in QS after the tilt challenge predicted wheeze at age 2–3 (Table 1). Inclusion of birth order (an indicator of risk of infection) in the models did not alter the effect estimates (i.e., a <10% difference). The association with acute changes in HR appeared to be present among girls (RR, 2.6 [95% confidence interval, 1.3–5.3]; $P = 0.006$) but not boys (RR, 1.2 [0.62–2.3]; $P = 0.60$) ($P_{\text{interaction}} = 0.023$; bivariate associations depicted in Figure 1).

Our hypothesis of an association between altered PSA in infancy and subsequent asthma was based on findings from our New York City birth cohort, where we observed that infants with rhinitis or watery eye symptoms in the absence of a cold were more likely to have exercise-induced wheeze, emergency department visits, and hospitalizations for asthma and other breathing problems when they reached school age (4). This association was independent of allergic sensitization and suggested a PSA connection between rhinitis or watery eyes in infancy and subsequent bronchoconstriction. The findings we report here offer some support for this connection, at least with regard to a preschool-age wheeze outcome. It is also compelling that the association between HR responses to tilt in newborns and wheeze in toddlers was only observed among girls. Increasingly, asthma is being conceptualized to be caused by complex heterogeneous pathological processes, some of which are independent of allergic inflammation but dependent on sex (10).

One limitation of this study is that wheeze (the result of airway narrowing) at age 2–3 years has multiple causes, some of which

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Table 1. Relative Risk for Wheeze at Age 2–3 Years with the Interquartile Range Increase in Heart Rate Variability at Baseline and Response to Tilt in Newborns in Active and Quiet Sleep

	Unadjusted RR*	Adjusted RR†
Active sleep baseline		
HF-HRV‡ ($n = 282$)	1.0 (0.88–1.1)	1.0 (0.89–1.2)
Active sleep response to tilt		
Acute response§ ($n = 254$)	1.1 (0.75–1.5)	1.1 (0.72–1.5)
Sustained response‖ ($n = 252$)	1.2 (0.88–1.5)	1.2 (0.88–1.5)
Quiet sleep baseline		
HF-HRV‡ ($n = 139$)	1.1 (0.94–1.3)	1.1 (0.95–1.3)
Quiet sleep response to tilt		
Acute response§ ($n = 173$)	1.7 (1.2–2.6)¶	1.8 (1.1–2.8)**
Sustained response‖ ($n = 178$)	1.5 (1.1–1.9)¶	1.5 (1.1–2.0)**

Definition of abbreviations: HF-HRV = high-frequency heart rate variability; RR = relative risk.
*Generalized estimating equations were used to calculate relative risks (95% confidence intervals).
†Models were adjusted for sex, gestational age, fetal alcohol and tobacco exposure, study location, and age at HRV measurement. HF-HRV models were additionally adjusted for the number of epochs averaged.
‡Variation in heart rate within the normal range of infant breathing rates using spectral analyses during the 10-minute baseline period before initiation of a tilt test.
§Acute heart rate responses to three head-up tilts (maximum − minimum HR during the first 15 s in the head-up position).
‖Sustained HRV responses to head-up tilt (median values during the 30-s period immediately before each tilt subtracted from median values during the last minute in the head-up position).
¶$P < 0.01$.
**$P < 0.05$.

are transient and others which develop into chronic disease. Thus, it will be important to better ascertain the causes of preschool-age wheeze in future studies, and to follow children to school age to examine associations between infant HRV and the development of chronic disease, including bronchial hyperreactivity. Second, multiple measures of HRV in different sleep states were made in this study, increasing the likelihood of spurious findings. Therefore, the findings of this study will need to be confirmed in future studies.

These preliminary findings suggest an association between measures of parasympathetic function, specifically indicators of a heightened vagal regulation, in the month after birth and wheeze later in childhood among girls. If these findings are validated in future studies designed to test these associations, they could indicate a connection between early-life autonomic nervous system regulation and the development of subsequent asthma-related symptoms. These observed associations appeared to be independent of variables commonly associated with allergic asthma (i.e., they were more common among girls and not modified by birth order). Further studies of the influence of early-life PSA on the risk of asthma development could contribute to our understanding of and therapeutic approach to this complex disease. ■

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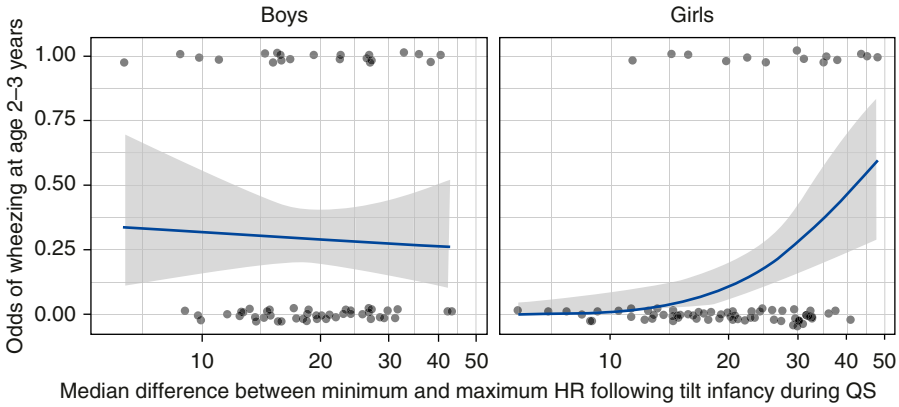

Figure 1. Acute change in heart rate (first 15 s) in response to tilt test during quiet sleep (QS) in infants and risk of wheeze at age 2–3 years, stratified by sex. Bivariate (unadjusted) associations are depicted in the figure. The blue line represents the odds ratio and the gray area represents the 95% confidence interval. HR = heart rate.

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Association between Pulmonary Hypertension and Clinical Outcomes in Hospitalized Patients with Sickle Cell Disease

To the Editor:

Pulmonary hypertension (PH) is a common complication of sickle cell disease (SCD) and is associated with increased morbidity and mortality in patients affected by SCD (1–3). Furthermore, SCD predominantly affects African Americans—a subgroup of patients that is associated with disparities in timely PH diagnosis and prognosis compared with other populations (4). However, the association between PH and clinical outcome and healthcare resource use in hospitalized African American patients with SCD is not known. We obtained data from a national cohort of patients with SCD who were hospitalized between 2003 and 2014 to determine the length of stay, postdischarge disposition, complication rate, and cost of hospitalization for inpatients with PH (SCD-PH) and without PH (SCD-noPH). Our data show that SCD-PH is an underrecognized cause of significant mortality and healthcare expenditures. This emphasizes the need for clinical care tracks and other strategies to prevent adverse clinical events and to improve healthcare efficiency for at-risk patients.

Methods

The U.S. National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project, contains deidentified data on patient demographics, insurance status, hospitalization characteristics, clinical comorbidities, and discharge disposition, as described in detail previously (5, 6). We searched the NIS database for hospitalizations between 2003 and 2014, and used *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9 CM) codes 282.41, 282.42, 282.60–282.64, 282.68, and 282.69 to identify all hospitalized patients ⩾18 years of age with a principal diagnosis of SCD and either African American or black race (6, 7). Patients for whom race information was not available (13.6% of the database) were excluded from further analyses. All patients who met the above criteria were then divided into two groups: those with a secondary diagnosis of PH (ICD-9 CM codes 416.0, 416.8, and 416.9; SCD-PH) (8) and those without PH (SCD-noPH). Using ICD-9 CM and clinical classification software codes, additional clinical comorbidities (dyslipidemia [53], tobacco use [V15.82, 305.1], and opioid dependence [304.00, 304.01–03, 304.70–73]), prior venous thromboembolism (VTE) (V12.51), acute stroke (430, 431, 434, 436), newly diagnosed VTE (415, 451, 453), acute chest syndrome (517.3), and invasive mechanical ventilation (96.70) were extracted. The outcomes were hospitalization duration, hospitalization cost, postdischarge disposition (e.g., nursing home or other circumspect postcare assistance), and in-hospital SCD clinical events (e.g., acute stroke, newly diagnosed VTE, acute chest syndrome, invasive mechanical ventilation, or in-hospital mortality).

Statistical analyses. The Pearson chi-square test for categorical variables and Student's *t* test or the Mann-Whitney *U* test (depending on the uniformity of distribution) for continuous variables were used to determine differences in hospitalizations between patients with SCD and those with SCD-PH. Multivariate logistic and linear regression models were constructed to analyze categorical (postdischarge disposition, acute stroke, newly diagnosed VTE, acute chest syndrome, invasive mechanical ventilation, and in-hospital mortality) and continuous outcomes (length of stay and hospitalization cost), respectively. The regression models were adjusted for the following covariates: age, sex, insurance status, median household income for residential zip code (in quartiles), calendar year, hospital characteristics (metropolitan location, bed size, and U.S. region), diabetes, dyslipidemia, hypertension, smoking, obesity, opioid dependence, alcoholism, heart failure,

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