Check for updates

ORIGINAL ARTICLE

Cerebral Autoregulation during Orthostatic Challenge in Congenital Central Hypoventilation Syndrome

Eric L. Vu[1,2,3]*, Emma C. Dunne[4]*, Allison Bradley[4], Amy Zhou[4], Michael S. Carroll[4], Casey M. Rand[3,4], Kenneth M. Brady[1,2,3,5], Tracey M. Stewart[4], and Debra E. Weese-Mayer[3,4,5]

[1]Division of Cardiovascular Anesthesia, Department of Anesthesiology, and [4]Division of Autonomic Medicine, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; [2]Department of Anesthesia, [5]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and [3]Stanley Manne Children's Research Institute, Chicago, Illinois

ORCID IDs: 0000-0001-6329-1931 (E.L.V.); 0000-0002-0526-7543 (M.S.C.); 0000-0002-4699-8940 (K.M.B.); 0000-0001-6061-220X (D.E.W.-M.).

Abstract

Rationale: Congenital central hypoventilation syndrome (CCHS) is a rare autonomic disorder with altered regulation of breathing, heart rate (HR), and blood pressure (BP). Aberrant cerebral oxygenation in response to hypercapnia/hypoxia in CCHS raises the concern that altered cerebral autoregulation may contribute to CCHS-related, variably impaired neurodevelopment.

Objectives: To evaluate cerebral autoregulation in response to orthostatic challenge in CCHS cases versus controls.

Methods: CCHS and age- and sex-matched control subjects were studied with head-up tilt (HUT) testing to induce orthostatic stress. Fifty CCHS and 100 control HUT recordings were included. HR, BP, and cerebral oxygen saturation (regional oxygen saturation) were continuously monitored. The cerebral oximetry index (COx), a real-time measure of cerebral autoregulation based on these measures, was calculated.

Measurements and Main Results: HUT resulted in a greater mean BP decrease from baseline in CCHS versus controls (11% vs. 6%; $P < 0.05$) and a diminished increase in HR in CCHS versus controls (11% vs. 18%; $P < 0.01$) in the 5 minutes after tilt-up. Despite a similar COx at baseline, orthostatic provocation within 5 minutes of tilt-up caused a 50% greater increase in COx ($P < 0.01$) and a 29% increase in minutes of impaired autoregulation ($P < 0.02$) in CCHS versus controls (4.0 vs. 3.1 min).

Conclusions: Cerebral autoregulatory mechanisms appear to be intact in CCHS, but the greater hypotension observed in CCHS consequent to orthostatic provocation is associated with greater values of COx/impaired autoregulation when BP is below the lower limits of autoregulation. Effects of repeated orthostatic challenges in everyday living in CCHS necessitate further study to determine their influence on neurodevelopmental disease burden.

Keywords: CCHS; neurocristopathy; orthostatic challenge; control of breathing; autonomic dysregulation

(Received in original form March 21, 2021; accepted in final form November 17, 2021)

*These authors contributed equally to this work.

Author Contributions: E.L.V.: substantial contributions to analysis and interpretation of data, drafting of work, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity. E.C.D. and A.Z.: substantial contributions to design of work and subject recruitment, drafting of work, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity. A.B.: substantial contributions to analysis of data, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity. M.S.C.: substantial contributions to analysis of data, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity. C.M.R.: substantial contributions to design of work and subject recruitment, drafting of work, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity. K.M.B.: substantial contributions to interpretation of data, drafting of work, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity. T.M.S.: substantial contributions to design of work and subject recruitment, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity. D.E.W.-M.: substantial contributions to study design, subject recruitment, interpretation of data, drafting of work, final approval, and agreement to be accountable for all aspects of work, including accuracy and integrity.

Correspondence and requests for reprints should be addressed to Eric L. Vu, M.D., Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Box 19, Chicago, IL 60611-2605. E-mail: ericvu@luriechildrens.org.

This article has a related editorial.

Am J Respir Crit Care Med Vol 205, Iss 3, pp 340–349, Feb 1, 2022
Copyright © 2022 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.202103-0732OC on November 17, 2021
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Congenital central hypoventilation syndrome (CCHS) is an autonomic disorder with altered regulation of breathing, heart rate, and blood pressure. There are limited data on cerebral oxygenation and cerebral autoregulation in this population.

What This Study Adds to the Field: This original research study of orthostatic challenge with head-up tilt testing was performed in a pediatric and young adult cohort with CCHS compared to a matched healthy control cohort. The cerebral oximetry index, a measure of autoregulation, was calculated with head-up tilt testing. With orthostatic stress, subjects with CCHS experienced, on average, a 2.3-fold greater decrease in mean blood pressure and 0.6× increase in heart rate from baseline compared to healthy controls. The lower limit of autoregulation or autoregulatory mechanism appears to be intact for subjects with CCHS; however, it is the greater hypotension observed in subjects with CCHS consequent to orthostatic provocation that is associated with greater values of cerebral oximetry index/impaired autoregulation.

Congenital central hypoventilation syndrome (CCHS) is a rare neurocristopathy characterized by autonomic nervous system (ANS) dysregulation, including impaired regulation of breathing, heart rate (HR), and blood pressure (BP) (1, 2). Caused by disease-defining *PHOX2B* gene mutations, CCHS presentation in the newborn period typically requires artificial ventilation. Affected individuals may experience periods of hypoxemia and hypercarbia at rest and in response to challenges of daily living, even with continuous artificial ventilation (3). The recurrent physiological compromise and innate CCHS-related autonomic dysregulation, coupled with altered cerebral regional blood flow/oxygenation during exogenous hypoxemia/hypercarbia challenges (4) and variably altered neurodevelopmental outcomes (5, 6), raise the concern that patients with CCHS may have altered patterns of cerebral autoregulation.

Cerebral autoregulation is the mechanism by which cerebral blood flow is regulated during changes in BP and cerebral perfusion pressure (7). Cerebral near-infrared spectroscopy (cNIRS) measures continuous, non-invasive, real-time cerebral oxygenation (regional oxygen saturation [rSO_2]), and this signal has been used to calculate indices of cerebral autoregulation. The cerebral oximetry index (COx) is a real-time measure of cerebral autoregulation that is calculated by correlating rSO_2 with mean BP (8–10). A high correlation between rSO_2 and mean BP, or positive COx values, is indicative of impaired autoregulation. Studies in adults report prolonged exposure of BP values below the lower limit of autoregulation (COx $>$ 0.3) to be associated with increased rates of stroke, prolonged mechanical ventilation, acute kidney injury, and mortality (11–14). COx has been validated and shown agreement with transcranial Doppler-derived measurements of pressure autoregulation in studies of piglets (8) and adult humans (13, 15, 16), but there have been no studies of COx in patients with CCHS.

Orthostatic challenges are designed to invoke an ANS-mediated baroreceptor reflex to induce compensatory changes to HR and BP. There have been limited studies of cNIRS with orthostatic challenge. In studies of adults with neurological diseases, orthostatic stress has been associated with abnormal cerebral tissue oxygenation in sepsis-associated brain dysfunction, age-related cerebromicrovascular dysfunction, and amnestic cognitive impairment (17–19). Considered in the context of abnormal cerebral rSO_2 responses to hypercapnia/hypoxia (4, 20), characterization of cNIRS and autoregulatory capacity in patients with CCHS during orthostatic challenge may elucidate unique physiological mechanisms in cerebral blood flow. Although there are various components to autoregulation (i.e., neurogenic) (21), this study focuses on pressure autoregulation during orthostatic challenge.

We hypothesized that patients with CCHS would have impaired cerebral autoregulation in response to orthostatic provocation relative to healthy control subjects. To test this hypothesis, head-up tilt (HUT) testing was utilized to induce an orthostatic challenge in patients with CCHS versus matched healthy control subjects, analyzing continuous recordings of HR, BP, and rSO_2. COx was derived as a measure of cerebral autoregulation. Results of these studies have been reported previously in abstracts (22–25).

Methods

Recruitment

From May 2011 to July 2019, healthy children (⩾6 yr) and young adults with CCHS undergoing standard-of-care, clinical HUT testing were included. In accordance with the 2010 American Thoracic Society Statement on CCHS, scheduled, physiological testing during sleep and activities of daily living were performed in the Autonomic Medicine clinical laboratory. Healthy control subjects were recruited from the Chicagoland area. Exclusion criteria for controls included conditions/symptoms of ANS dysregulation and medications known to affect ANS function. Age and sex matching was performed at a 1:2 ratio of CCHS to control tests. Recruitment proceeded with waiver of consent for clinical HUT testing and informed consent (and assent if age appropriate) obtained from legal guardians/subjects (institutional review board approval 2011–14412).

HUT Testing

Before testing, subjects were provided 28 oz of water. HUT was performed on a mechanical tilt table (WR Medical) in an autonomic testing room at constant ambient lighting and temperature (21°C). Testing included 10 minutes of baseline in supine horizontal position (baseline; time, −10 to 0 min), 10 minutes of physiological perturbation HUT at 70° incline (intra-tilt; time, 0–10 min), 2 minutes of recovery in supine horizontal position (post-HUT; time, 10–12 min). BP was measured (10 Hz) via continuous, noninvasive monitoring at the finger (Nexfin, Edwards LifeSciences). Recordings were also captured of three-lead ECG (10 Hz), HR (10 Hz), end-tidal carbon dioxide (Et_{CO_2}) (10 Hz), pulse oximetry (10 Hz) (WR Medical), and forehead cerebral rSO_2 (5 Hz) (Medtronic INVOS 5100C). During HUT testing, CCHS subjects requiring artificial ventilation via diaphragmatic pacer were instead supported with mechanical ventilation (to avoid pacer-induced artifacts on the ECG).

Analysis

Cerebral autoregulation was quantified by COx, a correlation coefficient between 10-second mean values of mean BP and rSO_2, calculated over 300 seconds and updated every 10 seconds in overlapping windows of time (8) (Figure 1). Epochs of 300 seconds were utilized because COx is a low-frequency phenomenon (0.003–0.05 Hz) (26), and impaired autoregulation was defined by COx > 0.3. Parameters were compared with multivariable linear regression, controlling for age, sex, height, and body mass index. Significance was defined as $P < 0.05$ (Wald test). Within-subject variability of variables was measured as standard deviation.

Significance in the variance of COx across mean BP was determined by a multiple linear regression model with generalized estimating equations and robust variance estimation. Generalized estimating equations were utilized to account for within-subject correlations with inconsistently repeated measures across BP ranges (27). Data are presented in 5-minute epochs of time to characterize the autoregulatory slow-wave response and in 1-minute epochs of time to characterize the immediate physiological response to the orthostatic challenge. Waveform analysis was performed with Matlab (R2020a, MathWorks) and statistical analysis with Stata 14 (StataCorp).

Results

Subjects

A total of 50 HUT tests in patients with CCHS and 100 HUT tests in control subjects were analyzed. Successful matching (1:2) by age and sex was achieved in the CCHS and control groups, with no significant differences demonstrated between groups; the mean age at testing in each group was 13.4 and 13.5 years, respectively (Table 1). With regard to ventilatory needs of this CCHS cohort, 52% had artificial ventilation needs while asleep only, 48% had artificial ventilation needs while awake and asleep (54% of whom had diaphragm pacing for awake support), 81% had a tracheostomy, and 48% were mechanically ventilated

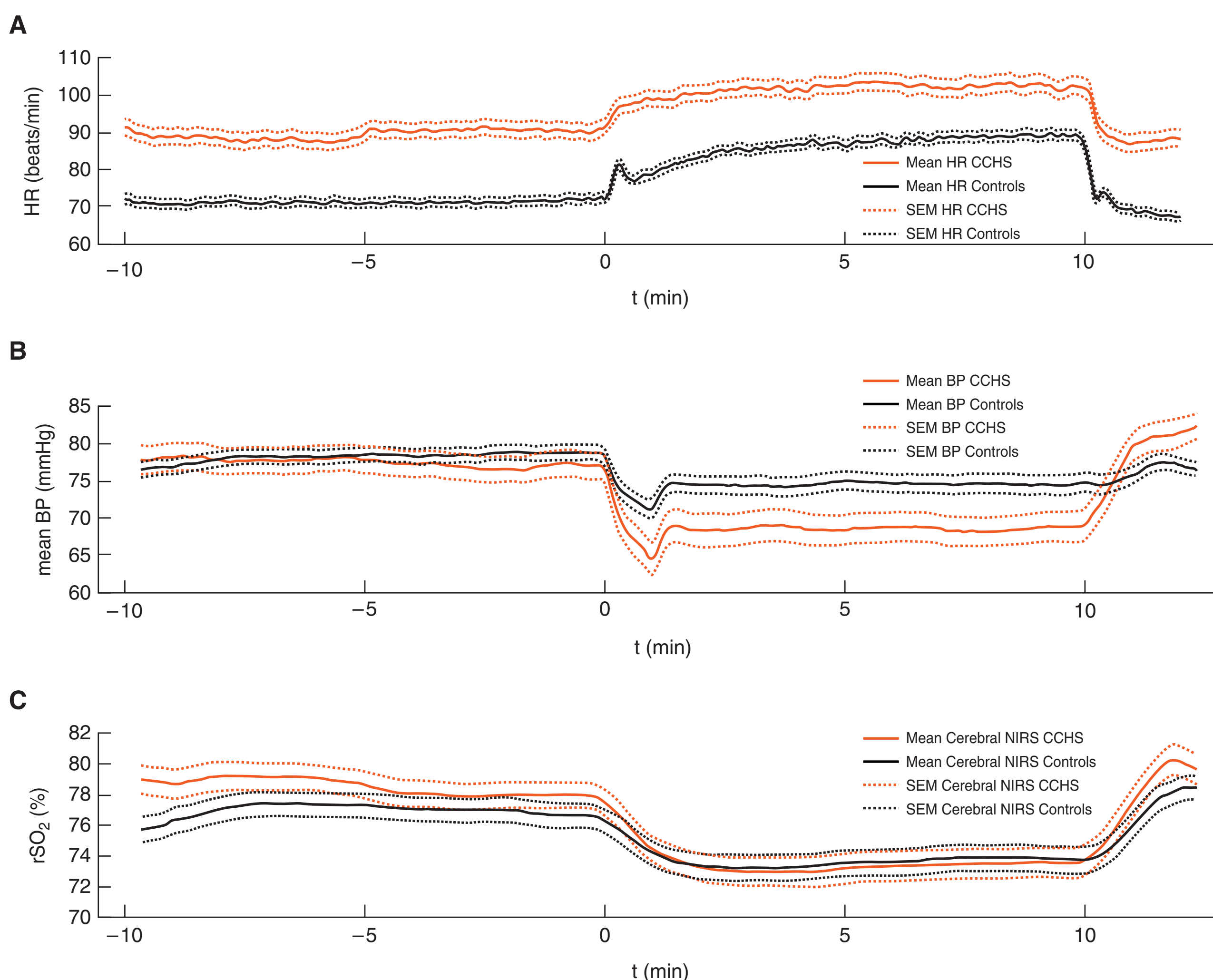

Figure 1. Overall physiologic response to head-up tilt in congenital central hypoventilation syndrome tests ($n = 50$) and control tests ($n = 100$) for (*A*) heart rate, (*B*) mean blood pressure, and (*C*) cerebral near-infrared spectroscopy during head-up tilt testing. Baseline period = time [−10 to 0 min]; tilt-up (70°) = time [0 min]; intra-tilt periods = time [0–5 min], [5–10 min], [0–10 min]; entire study period = time [−10 to 10 min]. BP = blood pressure; CCHS = congenital central hypoventilation syndrome; HR = heart rate; NIRS = near-infrared spectroscopy; rSO_2 = regional oxygen saturation; t = time.

Table 1. Characteristics of the Head-Up Tilt (HUT) Testing Cohort

	CCHS HUT Testing (*n* = 50)	Control HUT Testing (*n* = 100)	*P* Value
Sex, M	20 (40%)	40 (40%)	NS
Age, yr	13.4 ± 5.9	13.5 ± 5.9	NS
Height, cm	148.1 ± 17.2	151.7 ± 16.6	NS
Weight, kg	43.3 ± 16.9	46.0 ± 16.6	NS
20/25*	15 (30%)	—	—
20/26*	14 (28%)	—	—
20/27*	13 (13%)	—	—
NPARM; c.428A>G[†]	3 (6%)	—	—
NPARM; c.461G>C[†]	5 (10%)	—	—

Definition of abbreviations: CCHS = congenital central hypoventilation syndrome; HUT = head-up tilt; NPARM = non–polyalanine repeat expansion mutation; NS = not significant ($P > 0.05$).
Values are counts (percent) or mean ± SD.
*The CCHS-related *PHOX2B* genotype indicates the number of alanines on each allele for the PARMs 20/25, 20/26, and 20/27 (the normal genotype is 20/20; 20/25 indicates an extra five alanines on the affected allele, 20/26 indicates an extra six alanines on the affected allele, and 20/27 indicates an extra seven alanines on the affected allele).
[†]CCHS-related *PHOX2B* NPARMs indicate the specific missense variants c.428A>G (on exon 2) and c.461G>C (on exon 3).

during HUT testing (the remainder were breathing spontaneously). Of the patients with mechanical ventilation, 93% were consistently compliant with usage. In the CCHS cohort, 7% had a history of syncope, 37% had an implanted bipolar cardiac pacemaker because of cardiac conduction abnormalities (defined as sinus pauses of 3 s or longer), 14% had systemic hypertension, 7% had documented left ventricular dysfunction on transthoracic echocardiography, and 7% had a prior diagnosis of pulmonary hypertension. In addition, 26% had Hirschsprung disease, and 4% had a ganglioneuroma. During HUT testing, none of the CCHS or control subjects were syncopal; two adolescent girls with CCHS, but no control subjects, described pre-syncopal vision changes.

HUT Physiological Testing

During the 10 minutes of baseline recording, within-subject variability of physiological variables, including mean BP, HR, and rSO_2, was less than 10% in both groups. The physiological patterns in HR, mean BP, and rSO_2 between CCHS and control groups before, during, and after tilt-up are provided in Figure 1. As an example, COx signals from an 11-year-old female with CCHS are displayed throughout HUT testing; COx is derived from mean BP and rSO_2 signals (Figure 2).

At baseline, subjects with CCHS had a 28% higher mean HR and 34% lower HR variability compared with control subjects ($P < 0.01$; Table 2). There were no other differences in baseline characteristics in mean BP, rSO_2, or COx between the two groups. With tilt-up, subjects with CCHS experienced a greater decrease in mean BP compared with control subjects. In the first 1 minute after tilt-up, mean BP decreased 14% (13 mm Hg) from baseline in CCHS patient testing and 9% (7 mm Hg) from baseline in control subjects ($P < 0.05$; Table 3). Within the 0- to 5-minute window of tilt-up, mean BP decreased 11% (10 mm Hg) from baseline in the CCHS group and by 5.9% (4 mm Hg) from baseline in the control group ($P < 0.05$; Table 3).

Within the first minute after tilt-up, HR increased by 7.6% (6 beats/min) from baseline in subjects with CCHS and 10% (7 beats/min) from baseline in control subjects ($P < 0.01$; Table 2). In the 0- to 5-minute window after tilt-up, HR increased by 5.2% (12 beats/min) from baseline in subjects with CCHS and increased by 18% (18 beats/min) from baseline in control subjects ($P < 0.01$; Table 3). The remainder of mean and variability of HR and mean BP changes during HUT testing intervals are summarized in Tables 2 and 3, respectively.

Continuously recorded baseline (pre-HUT) peak and nadir Et_{CO_2} values were 43 (41–45) and 37 mm Hg (35–39), respectively, among CCHS subjects and 41 (41–42) and 36 (36–37) mm Hg, respectively, among control subjects. Intra-tilt peak and nadir Et_{CO_2} values were 44 (42–45) and 38 (37–40) mm Hg, respectively, among CCHS subjects and 41 (40–42) and 36 (36–37) mm Hg, respectively, among control subjects. Sp_{O_2} values were consistently 95% or greater in all subjects. There were no significant differences in Et_{CO_2} or Sp_{O_2} values between groups during these periods ($P > 0.05$).

Cerebral Oxygenation

Cerebral oxygenation during HUT testing is summarized in Table 4. There were no significant differences in absolute mean rSO_2 values between groups during HUT at any time interval. There were differences in intra-tilt variability in rSO_2 values at 0- to 1-minute and 0- to 5-minute epochs, but these differences are not clinically significant. Although no differences in COx between groups were observed at baseline (Table 5), after orthostatic challenge, subjects with CCHS experienced a 25% increase in COx values versus control subjects at 0–10 min (0.25 [0.17–0.32] vs. 0.15 [0.11–0.19], $P < 0.01$). The difference in COx is most pronounced in the first intra-tilt period (0–5 min), with an observed increase of 50% in COx values in CCHS subjects versus controls (0.39 [0.31–0.48] vs. 0.26 [0.20–0.32], $P < 0.01$). During HUT testing, subjects with CCHS experienced a 29% greater duration of time of impaired autoregulation (COx threshold of greater than 0.3) compared with control subjects (4.0 [3.3–4.6] vs. 3.1 [2.8–3.5] min, $P < 0.02$). COx was not calculated for epochs of time of less than 5 minutes because a minimum of a 5-minute window of time is required for derivation of one value of COx. The remainder of COx changes are summarized in Table 5. To observe the effect of BP change with HUT on autoregulation among subjects, mean COx values were binned by the mean BP change during the 0- to 5-minute intra-tilt period after tilt-up in the CCHS and control cohorts. Values of COx varied significantly across mean BP for subjects with CCHS and control subjects ($P < 0.02$); COx values greater than 0.3 occurred at lower mean BP when there was a BP decrease of more than 20 mm Hg with orthostatic challenge in the CCHS and control groups (Figure 3). Parameter estimates from the generalized estimation equation model for the relationships between mean BP and COx during HUT testing are summarized in Table 6.

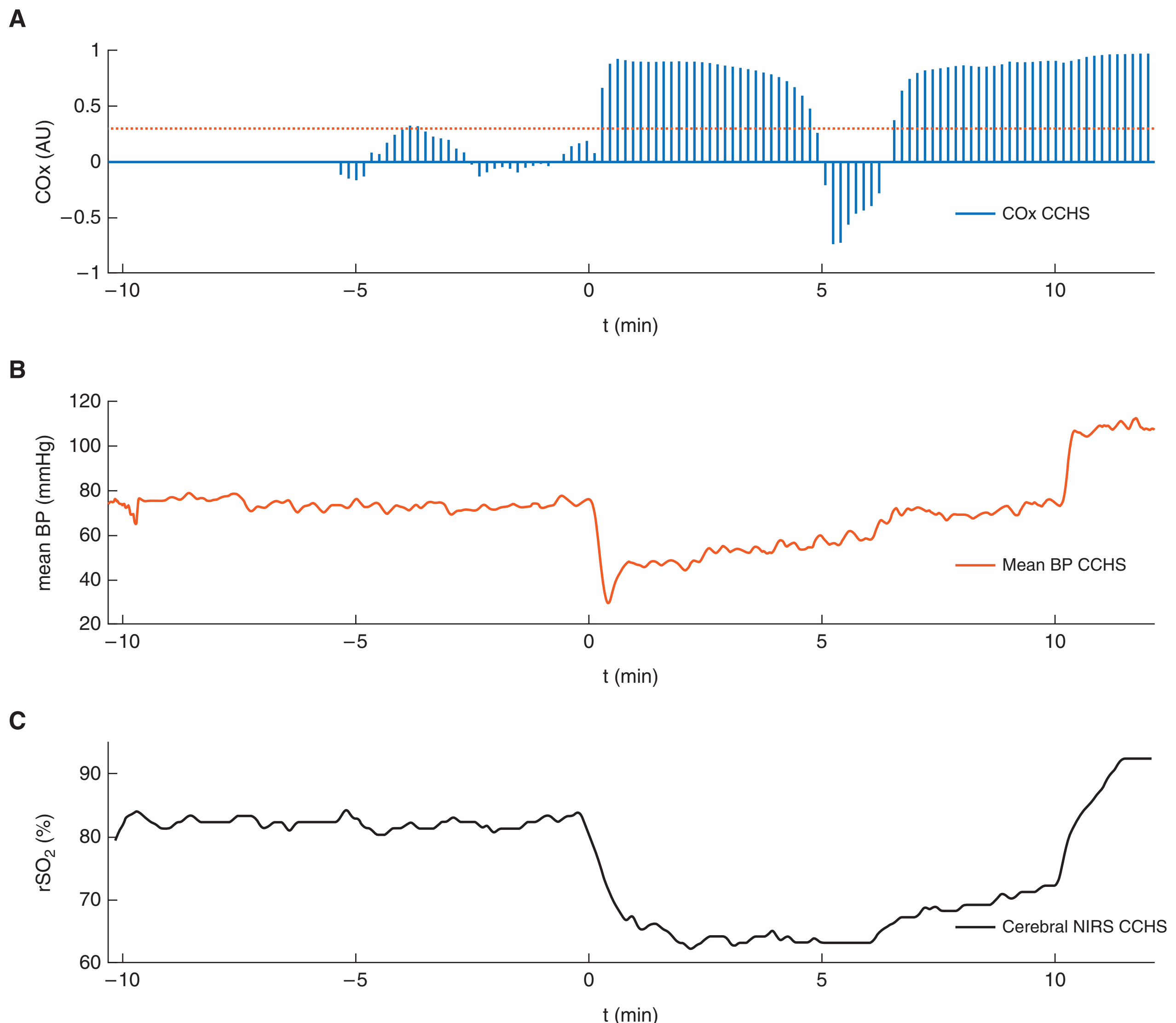

Figure 2. Representative cerebrovascular autoregulation signals in an 11-year-old female with congenital central hypoventilation syndrome during head-up tilt testing. (*A–C*) COx (*A*), mean blood pressure (*B*), and cerebral near-infrared spectroscopy (*C*); the horizontal red line in *A* indicates a cerebral oximetry index of 0.3 (values above indicate impaired autoregulation). Baseline period = time [−10 to 0 min]; tilt-up (70°) = time [0 min]; intra-tilt periods = time [0–5 min], [5–10 min], [0–10 min]; entire study period = time [−10 to 10 min]. AU = arbitrary unit; BP = blood pressure; CCHS = congenital central hypoventilation syndrome; COx = cerebral oximetry index; NIRS = near-infrared spectroscopy; rSO_2 = regional oxygen saturation; t = time.

Discussion

This study evaluated hemodynamic parameters and cerebral autoregulation in subjects with CCHS and control subjects during orthostatic challenge testing, and the results demonstrate a 29% increase in time of impaired autoregulation (COx > 0.3) in patients with CCHS compared with matched control subjects during HUT. This dysautoregulation was associated with the more extreme hypotension in the CCHS group during orthostatic stress so that subjects with CCHS experienced, on average, a 1.9-fold greater decrease in mean BP from baseline compared with healthy control subjects in the first 5 minutes after HUT. The association between mean BP decrement and COx is shown in Figure 3; the degree of hypotension experienced with HUT was greater in the subjects with CCHS. However, for both subjects with CCHS and control subjects, impaired autoregulation (COx > 0.3) was experienced when the hypotension nadir was greater than 20 mm Hg from baseline. Thus, the lower BP limit of autoregulation or autoregulatory mechanism appears to be intact for subjects with CCHS; however, it is the greater (more severe) hypotension observed in subjects with CCHS with orthostatic provocation that is associated with greater values of COx, indicating impaired cerebral autoregulation.

Because there are no studies of impaired autoregulation in pediatric patients, impaired autoregulation was defined by COx > 0.3, based on existing adult studies (11–14). COx measures vascular reactivity in response to arterial BP changes, not changes in

Table 2. Heart Rate during Head-Up Tilt Testing in Congenital Central Hypoventilation Syndrome and Control Subjects

Heart rate, beats/min	CCHS Tests (*n* = *50*)	Control Tests (*n* = *100*)	Adjusted Mean Difference	*P* Value
Baseline mean (−10 to 0 min)	91 (87–95)	71 (69–73)	18.7	<0.00001
Baseline variability (−10 to 0 min)	3.5 (3.1–3.9)	5.8 (5.3–6.3)	−2.3	<0.00001
Intra-tilt mean (0 to 1 min)	97 (93–101)	78 (76–80)	14.3	<0.00001
Intra-tilt variability (0 to 1 min)	4.8 (4.0–5.6)	6.8 (6.4–7.3)	−2.0	<0.00001
Change from baseline (0 to 1 min), %	7.6 (4.9–10)	10 (8.4–12)	−2.1	0.03
Intra-tilt mean (0 to 5 min)	101 (96–105)	84 (81–86)	16.6	<0.00001
Intra-tilt variability (0 to 5 min)	5.2 (4.6–5.8)	7.4 (7.0–7.7)	−2.1	<0.00001
Change from baseline (0 to 5 min), %	11 (8.3–14)	18 (16–21)	−4.9	0.01
Intra-tilt mean (5 to 10 min)	103 (98–108)	89 (86–91)	13.4	<0.00001
Intra-tilt variability (5 to 10 min)	4.2 (3.5–5.0)	6.5 (6.1–6.9)	−2.3	<0.00001
Change from baseline (5 to 10 min), %	14 (11–17)	26 (23–28)	−2.0	0.045
Intra-tilt mean (0 to 10 min)	100 (95–104)	83 (81–86)	15.7	<0.00001
Intra-tilt variability (0 to 10 min)	7.6 (6.7–8.5)	9.9 (9.3–11)	−2.0	<0.00001
Change from baseline (0 to 10 min), %	10 (7.5–13)	18 (16–20)	−1.8	0.02

Definition of abbreviation: CCHS = congenital central hypoventilation syndrome.
Values are mean (95% confidence interval).

metabolism. Thus, the results of this study pertain to pressure autoregulation, or the vascular reactivity in response to BP changes. The hypotension observed in patients with CCHS is of extreme relevance in a population that is vulnerable to autonomic dysregulation. To our knowledge, there have been limited HUT studies in the pediatric population and no prior studies that characterize cerebral autoregulation in CCHS with HUT testing. Previous work by Trang and colleagues (28) characterized BP and HR variability measurements in 12 16-year-old patients with CCHS versus 12 matched control subjects during HUT testing. At rest, the CCHS cohort demonstrated increased HR and reduced variability, in concordance with the findings of our study (Table 2). We report an exaggerated decrease in BP with tilt-up position in CCHS versus controls despite comparable water consumption prior to testing in both groups. We find it noteworthy that this BP decrement was not reported in the work of Trang and colleagues (28); it may be due to differences in study population (a younger age group in our cohort), longer testing conditions (10 min in our study vs. 5 min in the study by Trang and colleagues [28]) and greater degree of tilt (70° in our study vs. 60° in the study by Trang and colleagues [28]), variations in study design/measurement/size of epochs analyzed, or differences in disease management by site.

These results suggest that the vagal withdrawal and limitations in baroreflex response in CCHS result in a greater degree of hypotension that is associated with BP values below the lower limits of autoregulation. A previous study has demonstrated an association between blunted sympathetic responses and reduced cardiac baroreflexes in CCHS (28). We and others have suggested that patients with CCHS demonstrate diminished cerebral perfusion and blood oxygenation (4, 20). However, the physiological parameters of cerebral autoregulation have never been quantified in CCHS. Here we demonstrate that the cardiac vagal and sympathetic dysregulation of CCHS has autoregulatory implications. Our findings are supported by the functional magnetic resonance studies by Ogren and colleagues (29), who report that CCHS subjects demonstrate impaired time-distorted and muted central responses to the autonomic challenge of a Valsalva maneuver.

In our calculations of COx, we utilized a static method (relative blood flow changes in response to steady-state changes in BP) to characterize a rapid change (tilt-up). A model by Tiecks and colleagues (30) has been

Table 3. Mean Arterial Blood Pressure during Head-Up Tilt Testing in Congenital Central Hypoventilation Syndrome and Control Subjects

Mean arterial blood pressure, mm Hg	CCHS Tests (*n* = *50*)	Control Tests (*n* = *100*)	Adjusted Mean Difference	*P* Value
Baseline mean (−10 to 0 min)	78 (74 to 80)	78 (76 to 80)	1.2	0.47
Baseline variability (−10 to 0 min)	4.3 (3.8 to 4.8)	4.2 (4.0 to 4.5)	0.29	0.91
Intra-tilt mean (0 to 1 min)	65 (62 to 70)	71 (69 to 74)	−3.0	0.01
Intra-tilt variability (0 to 1 min)	9.8 (8.5 to 11)	7.5 (6.9 to 8.2)	4.0	0.0005
Change from baseline (0 to 1 min), %	−14 (−17 to −11.4)	−9 (−10 to −7.5)	−6.3	0.0009
Intra-tilt mean (0 to 5 min)	68 (64 to 72)	74 (72 to 76)	−2.5	0.01
Intra-tilt variability (0 to 5 min)	6.4 (5.8 to 7.0)	5.7 (5.3 to 6.2)	2.2	0.03
Change from baseline (0 to 5 min), %	−11 (−15 to −8.0)	−5.9 (−7.4 to −4.4)	−4.5	0.001
Intra-tilt mean (5 to 10 min)	69 (65 to 72)	74 (72 to 77)	−5.9	0.007
Intra-tilt variability (5 to 10 min)	4.8 (4.2 to 5.3)	4.7 (4.3 to 5.1)	0.084	0.80
Change from baseline (5 to 10 min), %	−11 (−14 to −7.2)	−4.6 (−6.9 to −2.3)	−7.6	0.04
Intra-tilt mean (0 to 10 min)	70 (67 to 74)	75 (72 to 76)	−4.0	0.05
Intra-tilt variability (0 to 10 min)	8.1 (7.0 to 9.1)	6.1 (5.6 to 6.6)	2.1	0.0001
Change from baseline (0 to 10 min), %	−8.3 (−11 to −5.6)	−4.8 (−6.5 to −3.1)	−4.7	0.02

Definition of abbreviation: CCHS = congenital central hypoventilation syndrome.
Values are mean (95% confidence interval).

Table 4. Cerebral Oxygenation Changes during Head-Up Tilt Testing in Congenital Central Hypoventilation Syndrome and Control Subjects

	CCHS Tests (*n* = *50*)	Control Tests (*n* = *100*)	Adjusted Mean Difference	*P* Value
Near Infrared Spectroscopy, rSO_2, %				
Baseline mean (−10 to 0 min)	78 (77 to 80)	77 (75 to 79)	1.8	0.08
Baseline variability (−10 to 0 min)	1.2 (1.0 to 1.3)	1.2 (1.1 to 1.3)	−0.07	0.44
Intra-tilt mean (0 to 1 min)	75 (73 to 76)	74 (73 to 76)	−1.2	0.8
Intra-tilt variability (0 to 1 min)	1.0 (0.80 to 1.3)	0.98 (0.87 to 1.1)	0.3	0.7
Change from baseline (0 to 1 min), %	−4.3 (−5.2 to −3.3)	−3.3 (−3.8 to −2.8)	−1.3	0.4
Intra-tilt mean (0 to 5 min)	73 (72 to 75)	74 (72 to 75)	−1.3	0.1
Intra-tilt variability (0 to 5 min)	1.5 (1.2 to 1.7)	1.2 (1.1 to 1.3)	0.27	0.049
Change from baseline (0 to 5 min), %	−6.0 (−7.3 to −4.7)	−4.5 (−5.1 to −3.8)	−1.4	0.4
Intra-tilt mean (5 to 10 min)	73 (72 to 75)	74 (72 to 76)	−1.5	0.3
Intra-tilt variability (5 to 10 min)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.0)	0.08	0.4
Change from baseline (5 to 10 min), %	−7.9 (−10 to −5.7)	−5.3 (−6.5 to −4.2)	−1.4	0.5
Intra-tilt mean (0 to 10 min)	74 (73 to 76)	74 (73 to 76)	−1.0	0.054
Intra-tilt variability (0 to 10 min)	2.8 (2.4 to 3.3)	2.0 (1.8 to 2.2)	0.90	0.0002
Change from baseline (0 to 10 min), %	−6.0 (−7.6 to −4.4)	−4.2 (−5.1 to −3.3)	−1.3	0.5

Definition of abbreviations: CCHS = congenital central hypoventilation syndrome; rSO_2 = regional oxygen saturation.
Values are mean (95% confidence interval).

proposed to measure dynamic autoregulation but ultimately concludes that calculation of dynamic autoregulation yields results similar to static methods. Carey and colleagues (31) utilized transcranial Doppler-derived measurements of middle cerebral artery blood flow (CBF) to characterize autoregulation with HUT in adults with a history of vasovagal syncope. In the study by Carey and colleagues (31), when the Tiecks model was utilized for spontaneous changes in BP, the correlation coefficients for the measured and model-predicted cerebrospinal fluid (CSF) velocities were similar, even at low extremes of CBF velocities and mean BP. We chose to utilize COx for our study because of greater utilization of this method and wider applicability of results in the autoregulation body of literature.

Despite these encouraging results, we identify limitations of this research. First, this study analyzed pressure cerebral autoregulation, and results should be interpreted in the context that the myogenic mechanisms of autoregulation, which may also play an important role in the autonomic dysregulation seen in CCHS, are not characterized. Second, we were unable to characterize autoregulation in the 2-minute recovery period after HUT (time, 10–12 min) because this timeframe was not a long enough interval for us to meaningfully analyze autoregulation with low-frequency COx methods. Third, we used indirect estimates of CBF through the cNIRS rSO_2 and estimated continuous BP readings through noninvasive measures, recognizing that use of cNIRS as a surrogate of CBF is well documented in the autoregulation literature (8, 13, 15, 16). In addition, noninvasive plethysmography methods for continuous BP measurements have been documented to have good correlation with invasive methods during clinical scenarios and HUT testing (32, 33). Fourth, we did not directly measure arterial carbon dioxide levels (Pa_{CO_2}) or CSF carbon dioxide levels in these patients. In previous animal studies, hypercarbia does not ablate autoregulatory response and only alters the lower limit of

Table 5. Cerebral Oximetry Index Changes during Head-Up Tilt Testing in Patients with Congenital Central Hypoventilation Syndrome and Control Subjects

	CCHS Tests (*n* = *50*)	Control Tests (*n* = *100*)	Adjusted Mean Difference	*P* Value
COx (AU)				
Baseline mean (−10 to 0 min)	0.08 (0.005 to 0.15)	0.047 (−0.002 to 0.096)	0.03	0.57
Baseline variability (−10 to 0 min)	0.14 (0.11 to 0.16)	0.16 (0.14 to 0.18)	−0.03	0.09
Intra-tilt mean (0 to 5 min)	0.39 (0.31 to 0.47)	0.26 (0.20 to 0.32)	0.14	0.006
Intra-tilt variability (0 to 5 min)	0.19 (0.17 to 0.20)	0.19 (0.17 to 0.20)	−0.001	0.07
Intra-tilt mean (5 to 10 min)	0.037 (−0.047 to 0.12)	0.044 (−0.00021 to 0.088)	−0.01	0.8
Intra-tilt variability (5 to 10 min)	0.21 (0.18 to 0.24)	0.16 (0.15 to 0.18)	0.05	0.003
Intra-tilt mean (0 to 10 min)	0.25 (0.17 to 0.32)	0.15 (0.11 to 0.19)	0.10	0.007
Intra-tilt variability (0 to 10 min)	0.32 (0.29 to 0.35)	0.28 (0.26 to 0.30)	0.04	0.011
COx time (min)				
Dysautoregulation (COx > 0.3)	4.0 (3.3 to 4.6)	3.1 (2.8 to 3.5)	0.9	0.010

Definition of abbreviations: AU = arbitrary unit; CCHS = congenital central hypoventilation syndrome; COx = cerebral oximetry index.
Values are mean (95% confidence interval).

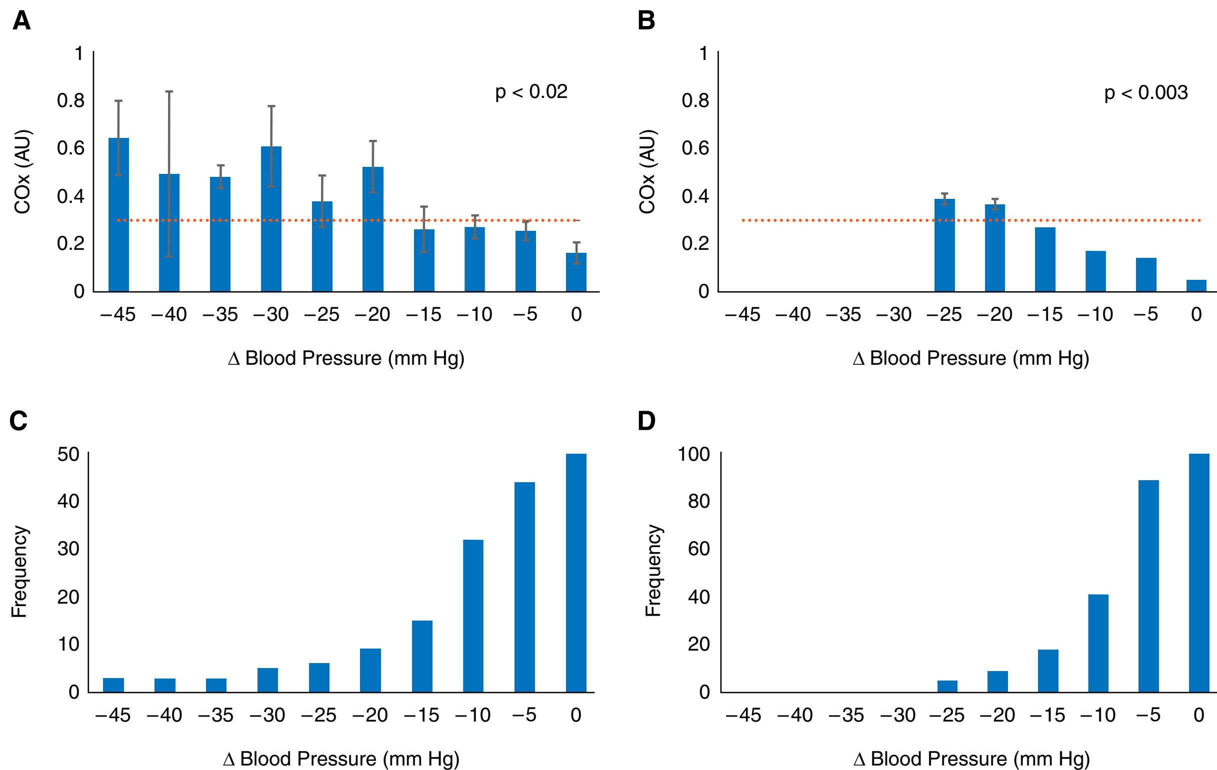

Figure 3. (*A* and *B*) Cerebral oximetry index binned by mean blood pressure change (Δ) from baseline (−10 to 0 min) compared with the 0- to 5-minute intra-tilt period in congenital central hypoventilation syndrome tests ($P < 0.02$) (*A*) and control tests ($P < 0.003$) (*B*). The horizontal red line indicates a cerebral oximetry index of 0.3 (values above indicate impaired autoregulation). (*C* and *D*) Histograms of binned observations for congenital central hypoventilation syndrome tests (*C*) and control tests (*D*). AU = arbitrary unit; COx = cerebral oximetry index.

autoregulation at extremely high levels of 75 mm Hg (34). In our study, the Et_{CO_2} levels were in physiological range in the CCHS and control groups, and although Pa_{CO_2} levels were not directly measured, they were likely similar in both groups. In addition, changes in Pa_{CO_2} levels in the CCHS group are chronic, and CSF CO_2 levels would have likely normalized beyond 6–24 hours of any acute Pa_{CO_2} change (21). Nonetheless, our study results suggest that the lower limit of autoregulation is similar in both groups (i.e., when mean BP falls 20 mm Hg from baseline). Finally, because CCHS is an exceedingly rare condition, and children need to be 6 years or older to participate in HUT testing, we relied on age at testing for the standard among CCHS patients and created a 1:2 age and sex match with control subjects rather than having 50 unique patients with CCHS who participated in HUT testing. Thus, the 1:2 ratio and utilization of number of tilt tests for comparison between groups was utilized to make meaningful comparisons in a disease population that is rare (35). This allowed us to have sufficient numbers for analysis. Although a limited number of patients experienced large BP decrements in both groups, the relationship between a greater drop in BP and positive COx was significant. Despite these limitations, this is the largest cohort of patients with CCHS to date who have been studied with HUT testing and measures of cerebral autoregulation.

Table 6. Parameter Estimates from the Generalized Estimating Equation Model of Relationship between Arterial Blood Pressure and Cerebral Oximetry Index during Head-Up Tilt Testing in Congenital Central Hypoventilation Syndrome and Control Subjects

	COx β (95% CI)	SE	*P* Value
CCHS			
Mean arterial blood pressure, mm Hg	0.0068 (0.0011–0.013)	0.0029	0.019
Control			
Mean arterial blood pressure, mm Hg	0.013 (0.0044–0.021)	0.0042	0.0027

Definition of abbreviations: CCHS = congenital central hypoventilation syndrome; CI = confidence interval; COx = cerebral oximetry index.
Values are β (95% confidence interval).

Conclusions

We performed hemodynamic characterization of the autoregulatory response in HUT testing among CCHS patients versus matched control subjects. In this study, the most notable finding is the exaggerated hypotensive response to HUT in CCHS. As a result of this hypotension, patients with CCHS are likely to experience a greater daily "dose" and more severe degree of cerebral dysautoregulation, presumably through a limited baroreflex response. The data generated here contribute to the understanding of cerebral hemodynamics with orthostatic provocation in a population vulnerable to impaired

cerebral blood flow. Future studies should determine the relationship between cerebral autoregulation and formal neurodevelopmental outcomes testing. With this approach, the links between the effects of chronically impaired autoregulation, neurocognition, and clinical status may be elucidated. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Medtronic for donating the cerebral NIRS probes for the healthy control subjects recruited for this study. The authors also thank the following invaluable individuals who participated in recruitment of healthy controls and completing the HUT testing: Molly Winston, Justin J. Warner, Lena J. Volpe, Brooke A. Pigneri, Drew Simon, Thomas Bielawiec, Samantha C. Gordon, Sally F. Vitez, Aaron Charnay, Stephen Joza, Kristen Kelly, Cia Panicker, Saajidha Rizvydeen, Grace Niewijk, Cara Coleman, Bradley J. Scher, David W. Reed, Sara M. Hockney, Gigi Buniao, Lynne Trojanowski, Cindy Brogadir, Michelle Price, and Anna S. Kenny.

References

1. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loghmanee DA, Trang H; ATS Congenital Central Hypoventilation Syndrome Subcommittee. An official ATS clinical policy statement: congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. *Am J Respir Crit Care Med* 2010;181:626–644.
2. Weese-Mayer DE, Rand CM, Zhou A, Carroll MS, Hunt CE. Congenital central hypoventilation syndrome: a bedside-to-bench success story for advancing early diagnosis and treatment and improved survival and quality of life. *Pediatr Res* 2017;81:192–201.
3. Kasi AS, Perez IA, Kun SS, Keens TG. Congenital central hypoventilation syndrome: diagnostic and management challenges. *Pediatric Health Med Ther* 2016;7:99–107.
4. Carroll MS, Patwari PP, Kenny AS, Brogadir CD, Stewart TM, Weese-Mayer DE. Residual chemosensitivity to ventilatory challenges in genotyped congenital central hypoventilation syndrome. *J Appl Physiol (1985)* 2014;116:439–450.
5. Zelko FA, Nelson MN, Leurgans SE, Berry-Kravis EM, Weese-Mayer DE. Congenital central hypoventilation syndrome: neurocognitive functioning in school age children. *Pediatr Pulmonol* 2010;45:92–98.
6. Charnay AJ, Antisdel-Lomaglio JE, Zelko FA, Rand CM, Le M, Gordon SC, *et al.* Congenital central hypoventilation syndrome: neurocognition already reduced in preschool-aged children. *Chest* 2016;149: 809–815.
7. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959;39:183–238.
8. Brady KM, Lee JK, Kibler KK, Smielewski P, Czosnyka M, Easley RB, *et al.* Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. *Stroke* 2007;38: 2818–2825.
9. Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, *et al.* Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. *Stroke* 2010;41:1957–1962.
10. Moerman A, De Hert S. Recent advances in cerebral oximetry: assessment of cerebral autoregulation with near-infrared spectroscopy: myth or reality? *F1000 Res* 2017;6:1615.
11. Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C, *et al.* Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. *Br J Anaesth* 2012;109:391–398.
12. Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y, *et al.* Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med* 2013;41:464–471.
13. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, *et al.* Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke* 2010;41:1951–1956.
14. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, *et al.* Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg* 2014;147:483–489.
15. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. *Neurocrit Care* 2009;10: 122–128.
16. Zheng Y, Villamayor AJ, Merritt W, Pustavoitau A, Latif A, Bhambhani R, *et al.* Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation. *Neurocrit Care* 2012;17: 77–84.
17. Crippa IA, Subirà C, Vincent J-L, Fernandez RF, Hernandez SC, Cavicchi FZ, *et al.* Impaired cerebral autoregulation is associated with brain dysfunction in patients with sepsis. *Crit Care* 2018;22:327.
18. Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am J Physiol Heart Circ Physiol* 2017;312:H1–H20.
19. Tarumi T, Dunsky DI, Khan MA, Liu J, Hill C, Armstrong K, *et al.* Dynamic cerebral autoregulation and tissue oxygenation in amnestic mild cognitive impairment. *J Alzheimers Dis* 2014;41:765–778.
20. Macey PM, Kumar R, Ogren JA, Woo MA, Harper RM. Images in sleep medicine: altered cerebral blood flow in a patient with congenital central hypoventilation syndrome. *Sleep Med* 2010;11:589–590.
21. Brady KM, Easley RB, Bissonnette B. Developmental physiology of the central nervous system. In: Gregory GA, Andropoulos DB, editors. Gregory's pediatric anesthesia. Chichester, UK: Wiley-Blackwell; 2012. pp. 117–138.
22. Vu E, Dunne E, Bradley A, Zhou A, Carroll M, Rand C, *et al.* Cerebral autoregulation during orthostatic challenge in congenital central hypoventilation syndrome (CCHS) vs. matched controls. Presented at the PAS 2021 Virtual Annual Research Conference. May 3, 20201, Philadelphia, PA. Poster Board 282.
23. Dunne EC, Zhou A, Carroll MS, Rand CM, Coleman C, Warner J, *et al.* Baroreceptor reflex and dynamic cerebral autoregulation during orthostatic challenge in healthy pediatric and young adult controls. Presented at the Pediatric Academic Societies Annual Research Conference. Toronto, Canada, May 2018.
24. Panicker C, Sadowski A, Rizvydeen S, Rand CM, Carroll MS, Kuntz NL, *et al.* Cerebral regional oxygen saturation during head-up tilt testing (HUT) in children and adolescents with postural orthostatic tachycardia syndrome (POTS) and matched controls. *Clin Auton Res* 2016; 26:334.
25. Carroll MS, Stewart TM, Brogadir CD, Kuntz NL, Kenny AS, Rand CM, *et al.* Cerebral regional blood flow/oxygenation, heart rate, and blood pressure responses in Congenital Central Hypoventilation Syndrome (CCHS) during head up tilt as compared to children referred with dizziness. *Clin Auton Res* 2013;23:243.
26. Fraser CD III, Brady KM, Rhee CJ, Easley RB, Kibler K, Smielewski P, *et al.* The frequency response of cerebral autoregulation. *J Appl Physiol (1985)* 2013;115:52–56.
27. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130.
28. Trang H, Girard A, Laude D, Elghozi J-L. Short-term blood pressure and heart rate variability in congenital central hypoventilation syndrome (Ondine's curse). *Clin Sci (Lond)* 2005;108:225–230.
29. Ogren JA, Macey PM, Kumar R, Woo MA, Harper RM. Central autonomic regulation in congenital central hypoventilation syndrome. *Neuroscience* 2010;167:1249–1256.

30. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995;26: 1014–1019.
31. Carey BJ, Manktelow BN, Panerai RB, Potter JF. Cerebral autoregulatory responses to head-up tilt in normal subjects and patients with recurrent vasovagal syncope. *Circulation* 2001;104:898–902.
32. Balzer F, Habicher M, Sander M, Sterr J, Scholz S, Feldheiser A, *et al.* Comparison of the non-invasive Nexfin® monitor with conventional methods for the measurement of arterial blood pressure in moderate risk orthopaedic surgery patients. *J Int Med Res* 2016;44:832–843.
33. Petersen ME, Williams TR, Sutton R. A comparison of non-invasive continuous finger blood pressure measurement (Finapres) with intra-arterial pressure during prolonged head-up tilt. *Eur Heart J* 1995;16: 1641–1654.
34. Nusbaum DM, Brady KM, Kibler KK, Blaine Easley R. Acute hypercarbia increases the lower limit of cerebral blood flow autoregulation in a porcine model. *Neurol Res* 2016;38:196–204.
35. Hennessy S, Bilker WB, Berlin JA, Strom BL. Factors influencing the optimal control-to-case ratio in matched case-control studies. *Am J Epidemiol* 1999;149:195–197.