

Temporal Trends of Cardiac and Respiratory Responses to Ventilatory Challenges in Congenital Central Hypoventilation Syndrome

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ABSTRACT

Congenital central hypoventilation syndrome (CCHS) patients exhibit respiratory deficits to ventilatory challenges, diminished breathing drive during sleep, and reduction of respiratory-related heart rate variation, but at least partially preserved peripheral chemoreception. We hypothesized that integration of afferent activity with respiratory motor output is deficient in CCHS, rather than chemoreceptor failure, and that examination of trends in heart and breathing rates and variabilities following ventilatory challenges may clarify the deficient mechanisms. Twelve children with CCHS and 12 age- and gender-matched control cases were subjected to hyperoxic hypercapnic, poikilocapnic hypoxic, and hyperoxic challenges while supine. Heart and respiratory rates and variabilities during 60-s baseline and 120-s challenge periods were assessed. Hypoxia and hypercapnia enhanced breathing rate in control subjects; in CCHS cases, the rise differed during hypercapnia and did not occur to hypoxia. Hyperoxia showed initial transient patterns in breathing rate that differed between groups. A heart rate increase to hypoxia and late decline to hyperoxia were muted in CCHS patients. In hypercap-

nia, heart rate followed similar rising patterns in both groups. Overall CCHS heart rate variability was lower in baseline and challenge periods, principally due to diminished respiratory-related variation, especially during hypercapnia. No heart rate variability group differences emerged in hypoxia, and only a late increase for CCHS cases developed in hyperoxia. The findings indicate retention of aspects of chemoreceptor sensitivity in CCHS cases. The heart rate alterations to ventilatory challenges suggest specific compensatory responses of a slower nature remain intact in CCHS, whereas other rapidly changing components are deficient. (*Pediatr Res* 55: 953–959, 2004)

Abbreviations

CCHS, congenital central hypoventilation syndrome
ECG, electrocardiographic
ET_{CO₂}, end-tidal CO₂
fMRI, functional magnetic resonance imaging
RMANOVA, repeated measures ANOVA
RSA, respiratory sinus arrhythmia

A number of alterations in respiratory and cardiovascular control characterize CCHS (also known as “Ondine’s curse”), including diminished ventilatory responses to CO₂ and hypoxia (1–4), a reduced drive to breathe during sleep (5), greatly diminished high frequency contributions to heart rate variability (6, 7), and abolition of cold pressor-induced respiratory changes (8). Despite these deficiencies, other respiratory and cardiovascular functions remain intact. CCHS patients can increase ventilation voluntarily in response to exercise, and to

passive motion of the extremities, even during sleep (9–12). Preservation of cardiovascular-related patterns include the slower heart rate variation induced by cold pressor stimulation, or induced by slower respiratory efforts accompanying Valsalva maneuvers (8). In addition, the spontaneous slow variation of heart rate that normally occurs in response to multiple sources during sleep is also present (5, 7), despite loss of faster respiratory-related influences.

The classical description of CCHS focuses on central chemoreceptor dysfunction (5, 13), however, components of both peripheral and central chemoreception appear to remain at least partially intact in CCHS. Respiratory rates increase in response to hypoxia and decline when subjects are exposed to hyperoxia (3, 14). Both children with CCHS and adults with central hypoventilation syndrome surgically induced by resection of

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medullary tumors arouse from sleep to hypercapnic stimulation (15, 16). Collectively, the evidence suggests retention of at least components of chemoreceptor afferent activity, that central components underlying respiratory motor output may be less affected, and that specialized deficits occur in the integration of sensory afferent inputs with breathing outputs, as previously proposed (3).

We hypothesized that integration of afferent activity with respiratory motor output remains the central deficit in CCHS, that this deficiency principally affects more rapidly changing components of breathing control, and that these processes can be revealed by examining rapid and slow cardiovascular and respiratory responses to ventilatory challenges. Particular challenges, such as hypercapnia which enhances respiratory sinus arrhythmia and variations in oxygen level, which alter heart rate variation at slower frequencies (17), should differentiate cardiovascular and respiratory responses in CCHS cases over controls and provide insights into deficient mechanisms.

We assessed the time course of heart and respiratory rates and variabilities to hypercapnic, hypoxic, and hyperoxic challenges with the objective of delineating failing central neural mechanisms that mediate these challenges in CCHS. Evaluation of the time course of responses to challenges was used to partition peripheral and central chemoreceptor action, as well as to determine longer-term cardiac and respiratory patterns.

METHODS

Subjects. Fourteen children with a diagnosis of CCHS and 15 control subjects participated in the study. Due to technical data-acquisition issues (lost or artifact-contaminated signals), a subset of 12 age- and gender-matched children from each group was used for the analysis (10 for heart rate during hypoxia). The mean age \pm SD (range) was 10.9 ± 1.9 (8–14) y for control subjects and 10.9 ± 2.4 (8–15) y for CCHS cases. Standard criteria (18) were used to establish the diagnosis of CCHS, and included ventilator dependency during sleep but not during wakefulness; absence of primary pulmonary, cardiac, or neuromuscular disease; and markedly reduced ventilatory responses to hypercapnia. We excluded CCHS cases with concomitant Hirschsprung's disease to avoid potential confounds from aberrant neural innervation to the viscera. All CCHS cases received a tracheostomy early in life for nighttime ventilation, however, these openings were occluded during waking hours and during the challenges. No control subjects had been subjected to this procedure. Physiologic assessments were made concurrently with fMRI procedures, so that brain structures involved in the ventilatory challenges could be visualized; those visualization studies will be reported separately. For all challenges, subjects lay supine in an MRI scanner. Baseline recordings were collected with subjects breathing room air for 60 s, after which the gas mixtures, hyperoxic hypercapnia (5% CO₂ in 95% O₂), poikilocapnic hypoxia (15% O₂, 85% N₂), or hyperoxia (100% O₂) were administered, each lasting 120 s, and separated by a minimum of 8 min.

Data acquisition and analysis. ECG and relative ET_{CO₂} measures were collected and stored. Digitizing rates for ECG

signals were 1 kHz, and 64 Hz for ET_{CO₂}. Cardiac RR intervals were measured from the ECG signal. Respiratory frequency and variability measures were derived from the ET_{CO₂} signal. Automatic peak-trough detection software was used to determine inspiratory and expiratory onset times. Detected peaks were reviewed on a digital display, which included raw signals and computer-selected inspiratory times, by an experienced observer who could evaluate and correct artifactual or erroneous detections, based on the context of other physiologic signals.

Cardiac intervals were plotted during the baseline and challenge conditions and compared, with RMANOVA, to evaluate group differences in heart rate and breathing rate during the recording periods, with comparisons between baseline and challenge for each group, and between groups during the challenge (19). A significance threshold of 0.05 was adopted. The challenge was divided into 12 10-s epochs, and the Tukey-Fisher criterion for multiple comparisons was used before testing for significance at individual epochs. Raw cardiac beat-to-beat intervals were successively plotted to optimally visualize momentary changes in variation and to display short-term and long-term patterns in heart rate. A measure of variation attributable to breathing, RSA, was determined by evaluating the extent of heart rate change per breath. For each breath, the corresponding trough-to-peak heart rate increase during and after inspiration and the magnitude of the subsequent peak-to-trough heart rate decrease corresponding to expiration were averaged to give the RSA for that breath. These values were assessed by RMANOVA and averaged over subjects within each group for display. Nonstationary aspects of the cardiac rate changes precluded assessment of variation with spectral analysis techniques.

In a subset of subjects (control $n = 10$ and CCHS $n = 7$), ET_{CO₂} was recorded during baseline and challenge conditions.

This study was approved by the institutional committee on human research; informed written consents were obtained from the subjects' caregivers.

RESULTS

Baseline. Mean baseline heart rate for control subjects (\pm SD) was 89.2 ± 12.6 beats/min, and for CCHS was 91.2 ± 12.9 beats/min (NS), as shown in Table 1; baseline respiratory frequency was 17.1 ± 4.7 breaths/min and 19.2 ± 3.7 breaths/min for control and CCHS subjects, respectively (NS). Variability (interquartile range) of heart rate for control subjects was 9.3 beats/min and 5.2 beats/min for CCHS cases ($p < 0.05$); respiratory rate variability for control subjects was 5.1 breaths/min and 4.3 breaths/min for CCHS cases (NS). In subsets of control and CCHS subjects, ET_{CO₂} was higher during baseline and challenge periods in CCHS cases (Table 1). ET_{CO₂} was higher during hypercapnia challenges in both groups (t test, $p < 0.05$), but was unchanged to hypoxia or hyperoxia.

Overall heart and respiratory rate variability. An overall diminished absolute heart rate variability in CCHS cases was apparent both during baseline and during all respiratory challenges. The reduced variability derived primarily from loss of

Table 1. Control and CCHS subjects' respiratory rate (BR), heart rate (HR), and, for a subset of subjects, ET_{CO_2} values averaged during 2-min challenge periods, and during baseline periods (\pm SD across subjects)

	BR		HR		ET_{CO_2}	
	Control	CCHS	Control	CCHS	Control (n = 10)	CCHS (n = 7)
Baseline	17.1 \pm 4.7	19.2 \pm 3.7	89.2 \pm 12.6	91.2 \pm 12.9	37.8 \pm 5	53 \pm 5.7
Hypercapnia	18.5 \pm 5.2	19.2 \pm 4.3	91.5 \pm 18.6	90.9 \pm 12.6	41.6 \pm 3.1	56.4 \pm 6.9
Hypoxia	17 \pm 5.4	19.7 \pm 4.1	89.8 \pm 9.7	93.6 \pm 14	37.5 \pm 3.5	52.4 \pm 4.8
Hyperoxia	19 \pm 8	19.4 \pm 4.9	90 \pm 18.4	92.4 \pm 13.2	36 \pm 4	49.2 \pm 3.3

more-rapid (principally respiratory-related) changes in heart rate, as displayed in the raw RR interval plots (Fig. 1) and in the average RSA plots (Fig. 2). Respiratory variability differences between groups were apparent during each challenge (Fig. 3).

Hypercapnia. In both groups, heart rates increased shortly after the challenge onset to CO_2 ($p < 0.05$, Fig. 4). The rise in both groups was biphasic, with a decline in cardiac frequency that emerged 30–40 s after onset of the hypercapnic stimulus. However, 60 s after hypercapnic challenge onset, CCHS cardiac rates increased again, whereas control subjects' rates remained low; toward the end of the challenge, heart rates increased in both control and CCHS groups. Mean heart rates were similar in both groups (Table 1). However, cardiac variability was enhanced in control subjects during the course of CO_2 administration (Fig. 3). This increase in variability primarily resulted from the much more prominent respiratory-related variation induced by hypercapnia in control subjects

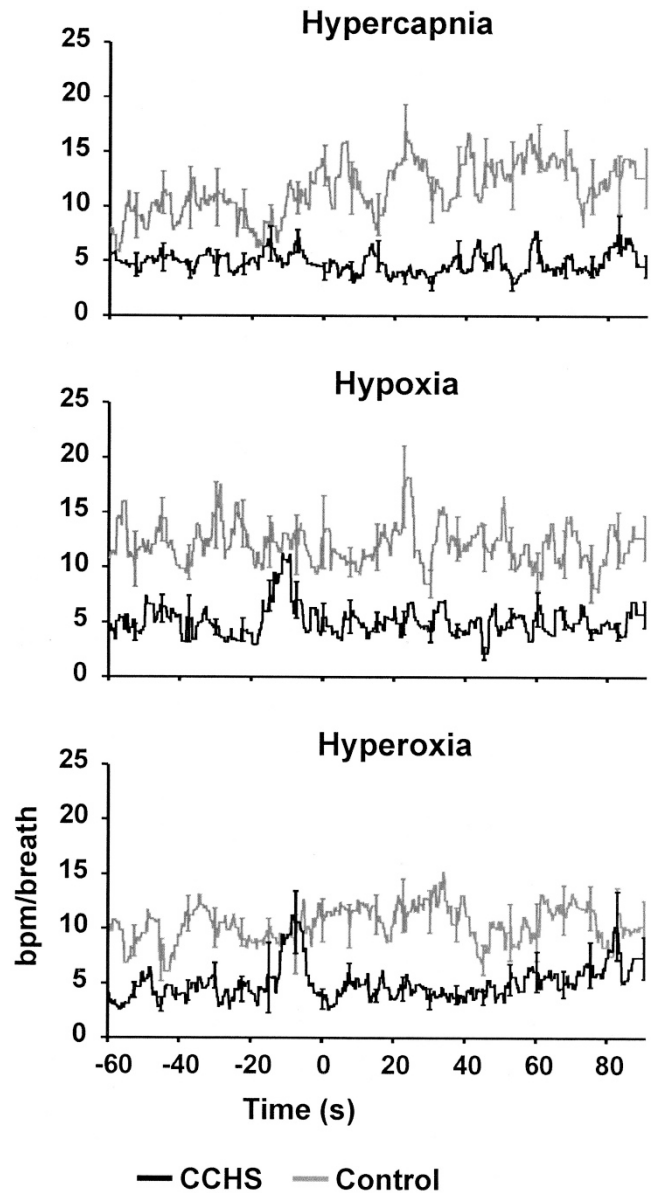


Figure 2. Average RSA values, with between-subject SE bars, for all CCHS and control cases are partitioned from other sources of variability and plotted over the course of each ventilatory challenge as variation in cardiac beats/min (bpm) per breath.

(Fig. 2); slower trends also contributed (Figs. 1, 2, and 5). Only modest changes occurred in CCHS patients.

Hypoxia. Control subjects increased respiratory rates to hypoxia late (60 s) in the challenge, but rates did not rise in CCHS cases (Fig. 4). Heart rates increased to hypoxia in both groups; the increase was less pronounced in CCHS than control

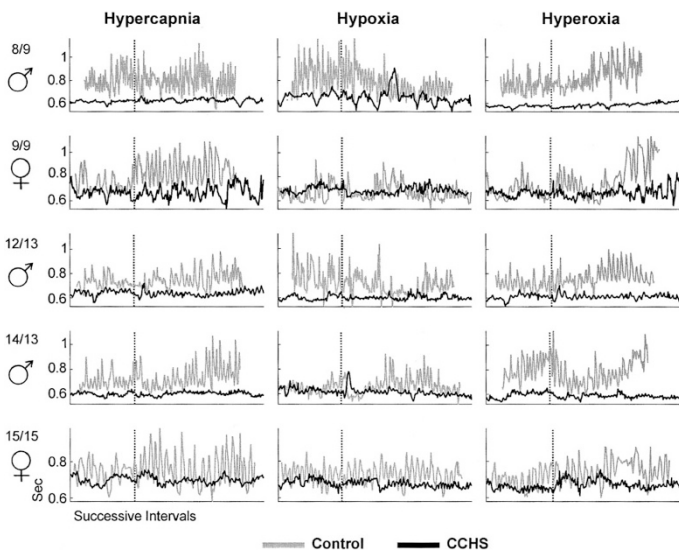


Figure 1. Plots of successive cardiac RR (interbeat) intervals, with interbeat interval period represented on the y axis (in seconds), and count of interval period represented on the x axis for five typical individual control subjects (gray traces) and five age- and gender-matched CCHS cases (black traces) during the 60-s baseline and 120-s ventilatory challenges. Gender for each matched pair is indicated to the left of the hypercapnia y axis as are the ages, in years, for subjects in each pair of control/CCHS subjects. Onset of challenge is indicated by the vertical dashed line in each trace. The length of each trace varies, because the successive number of intervals is represented on the x axis (rather than time); shorter intervals (*i.e.*, faster heart rates), being more numerous for the fixed time period of 150 s, are represented by longer traces. Hypercapnia (hyperoxic hypercapnia: 3% CO_2 , 95% O_2); Hypoxia (poikylotapnic hypoxia: 15% O_2 , balance, N_2); and Hyperoxia (100% O_2).

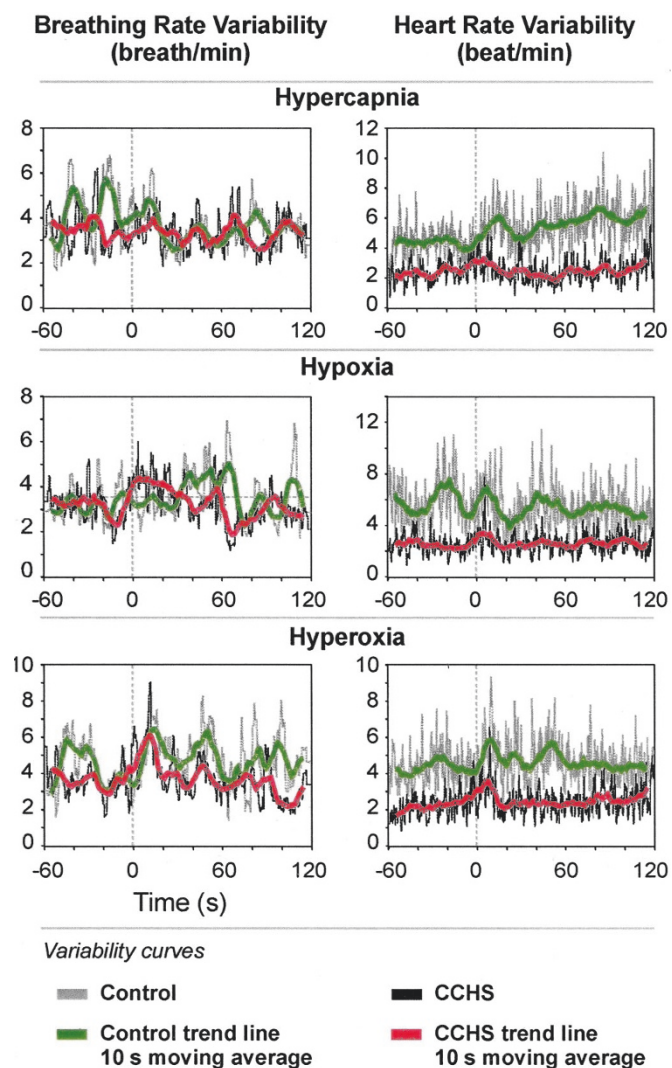


Figure 3. Average breathing and heart rate variabilities, together with 10-s moving average trend lines during the three challenges, with *black traces* representing CCHS case values and *gray traces* representing control subject values. Ten-second moving average trend lines are drawn for each group (CCHS, *red*; control, *green*). Challenge onset is at time 0 s (*vertical dashed line*), after 60 s of room air baseline.

subjects. No differences in change in heart rate variability were found between groups (Fig. 5). Respiratory variability increased in control subjects concurrently with the rise in breathing rate; CCHS cases showed a rise in respiratory variability only early in the challenge.

Hyperoxia. A momentary increase in respiratory rate developed during the first 10 s of the challenge in response to hyperoxia in control subjects (Fig. 4). The CCHS cases showed a comparable transient effect in the opposite direction. Respiratory rates later declined in both groups, but only transiently in control subjects. Heart rate initially increased, but later declined in both groups. The extent of increase and decrease in heart rate was significantly greater in control than in CCHS cases. Respiratory variability was higher during hyperoxia in control than in CCHS cases, but heart rate variability showed only a transient small increase, comparable across both groups, with the groups differing only at the end of the challenge (Fig. 5).

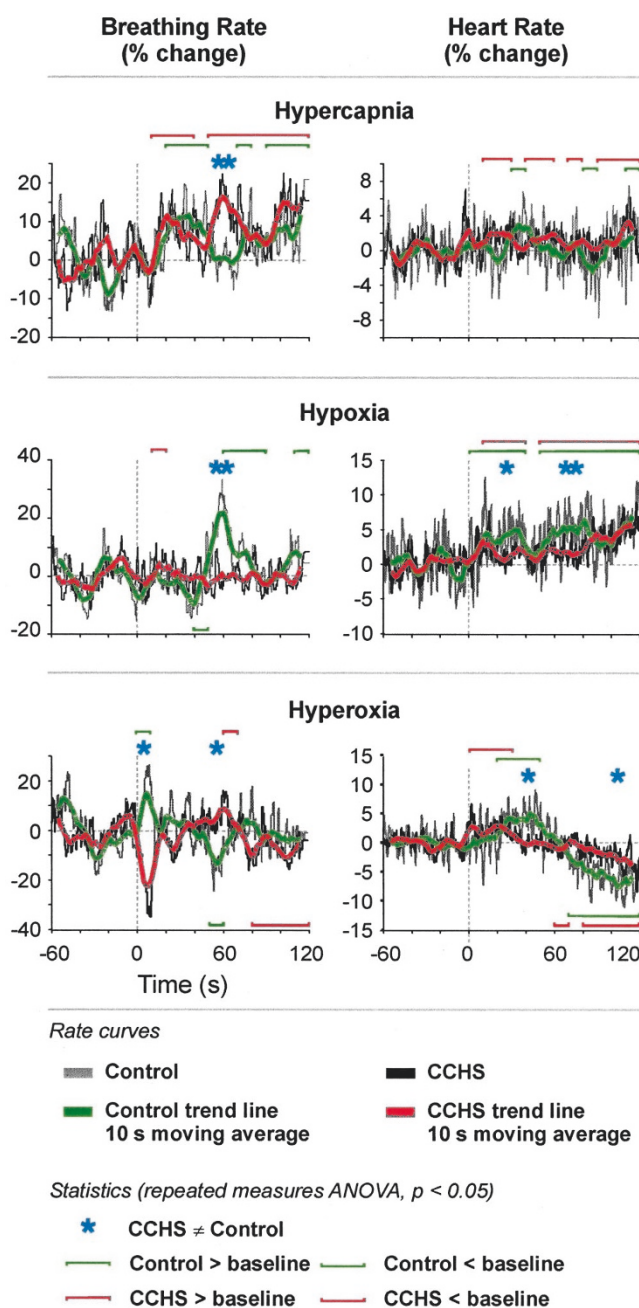


Figure 4. Traces of averaged percentage change in breathing and heart rates, together with trend lines, over baseline and during hypercapnic, hypoxic, and hyperoxic challenges, with color coding of traces and starting point indications as in Figure 3. Significant changes from baseline are represented in colored lines above or below the traces over relevant epochs (*red*, CCHS; *green*, control); significant differences between groups are indicated by *blue asterisks*, similarly placed over appropriate epochs.

DISCUSSION

A marked similarity of change in heart rate patterns emerged in both groups to the challenges, despite the large overall difference in heart rate variability. CCHS cases, however, showed substantially reduced rapid, respiratory-related cardiac variation during baseline and during challenges, and especially during hypercapnia, which enhanced RSA in control cases. Distinct respiratory patterns also emerged, particularly during hypoxia, with the CCHS patients not showing the expected rise

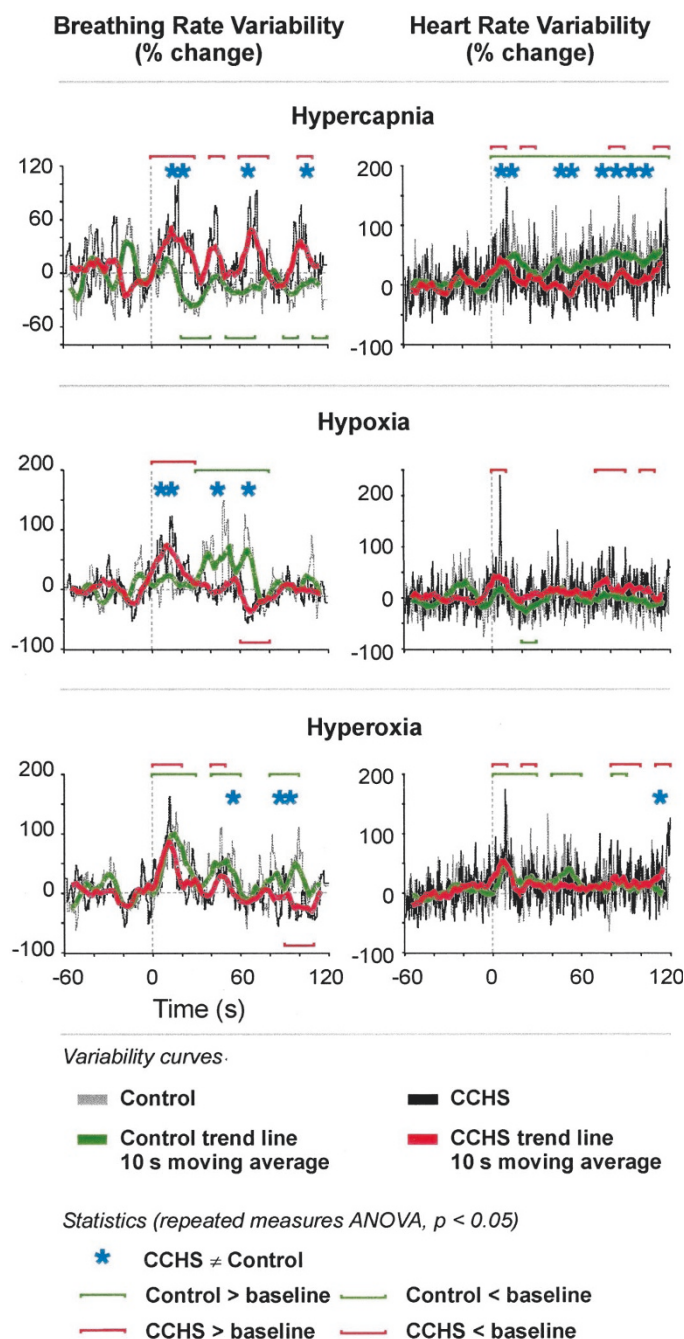


Figure 5. Average percentage change in breathing and heart rate variabilities (in percentage change from baseline) over each baseline and challenge period, with color-coding of traces, trend lines, epochs of significant effects, and start time indications as in Figure 4.

in breathing rate. However, although the time course of respiratory responses to hypercapnia in CCHS cases differed, breathing rates rose in both groups, and CCHS heart rates followed similar patterns to those of control subjects throughout the 120 s challenge period. The respiratory and cardiac rate responses to the ventilatory challenges reinforce evidence suggesting that CCHS respiratory deficits cannot be interpreted as a simple failure of central or peripheral chemoreception.

Although CCHS patients showed transient early respiratory rate differences from control subjects to hyperoxia, heart rate declined in a similar fashion, with only momentary pattern

differences. Moreover, although CCHS cases did not respond appropriately with respiratory rate adjustments to hypoxia, heart rates rose in a manner similar to the control subjects, even if more slowly. The findings suggest a degree of sensitivity to low oxygen and some retention of appropriate components of the cardiovascular response. Furthermore, although the time course of respiratory responses to hypercapnia in CCHS cases differed, breathing rates rose in both groups, and CCHS heart rates followed similar patterns to those of control subjects throughout the 120-s challenge period. The heart rate responses, together with current and previously demonstrated respiratory responses to cold pressor and volitional breathing exercises, suggest that deficient processes in CCHS ventilatory control are largely separate from slower integrative components and voluntary influences, and that these deficiencies relate principally to rapid integration of stimuli, resulting in abnormal respiratory musculature output.

Diminished overall variation in cardiac rates for CCHS cases was apparent in all baseline conditions, and the substantial differences in overall variability remained unchanged after administration of all challenges. Heart rate variability, principally from respiratory-related sources, increased even further in control subjects over the course of the hypercapnic challenge; the enhanced RSA to hypercapnia has been previously demonstrated by others in control subjects (20), and appears to be a mechanism to increase the efficiency of pulmonary circulation (21, 22). The failure of CCHS cases to increase RSA to hypercapnia represents one more deficit in central chemoreceptor integration with appropriate cardiovascular action (23). A reduction of RSA under resting conditions in CCHS has been a consistent finding in baseline recordings, particularly during sleep (6, 7), and after pressor challenge conditions (8).

Peripheral oxygen afferent processing. An initial transitory respiratory rate response emerged to hyperoxia in both control and CCHS cases, but the direction of these responses differed, with an increase in control cases and a decrease in CCHS patients. The underlying mechanism of the transitory responses to elevated oxygen tension is unclear. The transient responses occurred within 10 s, and were at the time limits of mediation by carotid body receptors. Increased concentrations of inspired CO_2 can stimulate CO_2 or pH sensors in the upper airway and mucosa independently of the peripheral chemoreceptors; this afferent activity is mediated by the superior laryngeal nerve (24). Comparable stimulation of upper airway chemosensory pathways in humans has been indicated by others (25), and suggests the potential for modification of respiratory patterns by airway stimulation. Thus, the immediate transient responses could have resulted from a neural reflexogenic response to inactivation of intra-airway peripheral chemoreceptor sensors in control cases (26), the latter sensors being dysfunctional in CCHS (27).

The later respiratory and cardiovascular responses to hypoxia and hyperoxia were of particular interest. Hyperoxia, through suppression of tonic peripheral chemoreceptor activity, would normally lead to a reduction in ventilation, whereas hypoxia would usually lead to enhanced ventilatory output by stimulating these chemoreceptors. Although CCHS patients, unlike control subjects, did not increase breathing rates to the

hypoxic challenge, heart rates responded near normally. Because CCHS cases responded with near-adequate respiratory and heart rate changes to hyperoxia, it is likely that peripheral chemoreceptor functions are partially preserved, as previously indicated (14). The current findings suggest the ability, in CCHS cases, to induce suppression of tonic chemoreceptor action, such that the response to hyperoxia appears to be appropriately mediated (3, 14). Hypoxia is normally accompanied by increased peripheral chemoreceptor afferent activity (28). In contrast to hyperoxic responses, the failure to appropriately increase respiratory rates to hypoxia in CCHS cases suggests deficits of some component of the respiratory control circuit. However, the relatively rapid adjustment of heart rate to hypoxia further indicates adequate afferent input from the periphery, and successful integration of those inputs within neural cardiovascular system pathways. Thus, it is likely that particular brainstem or even more rostral brain regions that preferentially relay processes for integrative respiratory activity are the regions that are most affected in CCHS, a possibility that is supported by the classical phenotypic manifestations of the disorder.

Trigeminal and voluntary influences. Stimulation of trigeminal afferents mediating certain sensory-related inputs results in different respiratory response patterns in CCHS compared with control children. For example, cold pressor application to the forehead enhances respiratory efforts in control but not in CCHS subjects (8). Our challenges bypassed trigeminal sensors of the nasal passages, because the subjects wore nose clips, but trigeminal mediation of stimulation of the oropharynx was still a possibility. The issue of airway reflexogenic stimulation needs to be further explored in CCHS. Low-frequency heart rate patterns associated with exaggerated voluntary expiratory efforts or appearing with forehead cold pressor challenges are retained in CCHS (8), even when faster variation from spontaneous breathing is diminished. Thus, ventilatory and reflexive cold pressor responses of a slow nature or of a voluntary characteristic appear to be retained in CCHS, whereas rapidly changing aspects of trigeminal influences and selective components of hypoxic and hypercapnic-related responses are markedly reduced.

Neural mechanisms. Because voluntary breathing efforts are relatively unaffected in CCHS (8), it is unlikely that ventral frontal cortical areas, which regulate the upper airway and show damage in other breathing disorders (29), or brainstem projections from that region are affected. Because peripheral chemoreception is at least partially retained, afferent projections to the nucleus of the solitary tract are likely intact. Afferent proprioceptive activity from the lower limbs likely contributes to respiratory enhancement in CCHS during exercise, inasmuch as passive cycling of the foot during sleep reestablishes ventilation (9). The most likely integrative site for that stimulation lies in cerebellar deep nuclei, influenced by overlying cerebellar cortex, which receives proprioceptive information to coordinate motor output. Peripheral limb motion accompanying exercise has long been known to couple with respiratory efforts (30, 31), and proprioceptive information plays an essential role in that coordination (32). The cerebellar fastigial nucleus shows significant responses to CO₂ exposure

(33) and plays a major role in vagally mediated respiratory reflexes (34); damage to the nucleus results in an inability to cope with extremes of blood pressure changes (35). We speculate that damage to cerebellar fastigial nuclei, or to overlying cortical projections to these nuclei, leads to the impairment of rapid cardiac responses in CCHS to hypercapnia and hypoxia shown here, and the diminished drive to breathe that occurs during sleep. The means by which the fastigial nucleus might restore breathing during sleep in CCHS through cyclic leg movements are speculative, but may result from exaggerated proprioceptor activity to cerebellar cortex or deep nuclei arising from that movement. Restoration of regularity in breathing in normal infants can be accomplished by other cerebellar input, *e.g.* vestibular action through rocking (36).

Future studies. The possibilities that rapid-coordination of breathing efforts with cardiovascular action is mediated by cerebellar structures, and that damage to these structures results in CCHS characteristics, are readily testable. Cerebellar structures show functional responses to hypercapnic challenges, and respond to loaded breathing or pressor challenges on fMRI examination (37, 38). Structures that are normally recruited to ventilatory challenges in the cerebellum show functional deficits in preliminary studies of CCHS cases (37, 39). Examination of cerebellar neural responses to ventilatory challenges following increased proprioceptive drive in CCHS cases should show compensatory enhancement of those neural responses, as well as more-appropriate physiologic responses. Damaged cerebellar cortical projections to fastigial nuclei in a chronic (*i.e.* drug-free) animal preparation should show a loss of drive to breathe during sleep, a loss of respiratory-related heart rate variation, and impaired responses to blood pressure manipulation. Damage to this nucleus has been examined in anesthetized preparations (35), with findings of significant deficits to pressor challenges.

Limitations. These studies have several limitations. Respiratory rate contributes only a portion of minute ventilation, inasmuch as timing and amplitude of breathing are controlled by different mechanisms. CCHS patients tend to maintain a relatively constant tidal volume, and characteristically modify minute ventilation almost exclusively by changing respiratory rate (11). This pattern is in contrast with control subjects who modify minute ventilation by altering both respiratory frequency and tidal volume. These differences could play a role, albeit minor, in the cardiac and respiratory variability differences found between CCHS and control cases. In addition, as opposed to previous studies that were carried out in the upright or seated positions, these studies were conducted in the supine position for both groups. Body positional differences may modify both cardiovascular and respiratory response characteristics (40). This issue is of particular relevance to the cardiovascular measures, because blood pressure aspects are closely related to vestibular influences and other postural mechanisms (41). It is the case that all CCHS subjects breathed at night through a tracheostomy, unlike controls. Adaptation to reduced stimulation of the oral airway through loss of airflow during sleep may have altered afferent processes in CCHS cases to these challenges in the waking state. We consider that possibility not likely, because the tasks were administered

during conditions when the tracheostomy was closed during the waking state, but the potential for such adaptation cannot be excluded.

CONCLUSIONS

The findings suggest that simplistic concepts of CCHS characteristics being attributed to deficits in central and peripheral chemoreceptor responsiveness are inadequate. Slower-acting cardiovascular changes, likely providing compensatory perfusion, remain largely intact in CCHS, whereas more rapidly changing influences on heart rate variability are severely affected. Although muted, the cardiac responses to hyperoxia, combined with selected near-adequate cardiac rate responses to hypoxia and hypercapnia, emphasize that respiratory/cardiac control in CCHS has unique, fast-response insufficiencies. Chemoreceptor sensitivity remains functional in CCHS; however, that sensitivity is not reflected in normal breathing or heart rate variability responses, and implicates integrative deficits, rather than sensory deficits *per se*.

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