0031-3998/92/3101-0291$03.00/0
PEDIATRIC RESEARCH

Vol. 31, No. 3, 1992
Printed in U.S.A.

Heart Rate Variability in Congenital Central Hypoventilation Syndrome

MARLYN S. WOO, MARY A. WOO, DAVID GOZAL, MARY T. JANSEN, THOMAS G. KEENS, AND RONALD M. HARPER

Childrens Hospital of Los Angeles [M.S.W., D.G., M.T.J., T.G.K.], Los Angeles, California 90054-0700 and Division of Cardiology [M.A.W.] and Department of Anatomy and Cell Biology [R.M.H.], University of California, Los Angeles, California 90024

ABSTRACT. Heart rate variability was assessed in 12 patients with congenital central hypoventilation syndrome (CCHS) and in age- and sex-matched controls using SD of time intervals between R waves (R-R intervals), R-R interval histograms, spectral analysis, and Poincaré plots of sequential R-R intervals over a 24-h period using ambulatory monitoring. Mean heart rates in patients with CCHS were 103.3 ± 17.7 SD and in controls were 98.8 ± 21.6 SD ($p > 0.5$, NS). SD analysis of R-R intervals showed similar results in both groups (CCHS 102.2 ± 36.0 ms *versus* controls 126.1 ± 43.3 ms; $p > 0.1$, NS). Spectral analysis revealed that, for similar epochs sampled during quiet sleep and wakefulness, the ratios of low-frequency band to high-frequency band spectral power were increased for 11 of 12 patients with CCHS during sleep, whereas a decrease in these ratios was consistently observed in all controls during comparable sleep states ($\chi^2 = 20.31$; $p < 0.000007$). During wakefulness, the ratios of low-frequency band to high-frequency band spectral power were similar in both patients with CCHS and controls. Poincaré plots displayed significantly reduced beat-to-beat changes at slower heart rates in the CCHS patients ($\chi^2 = 24.0$; $p < 0.000001$). The scatter of points in CCHS Poincaré plots was easily distinguished from controls. All CCHS patients showed disturbed variability with one or more measures. The changes in moment-to-moment heart rate variability suggest that, in addition to a loss of ventilatory control, CCHS patients exhibit a dysfunction in autonomic nervous system control of the heart. (*Pediatr Res* 31: 291–296, 1992)

Abbreviations

CCHS, congenital central hypoventilation syndrome
HRV, heart rate variability
R-R, time interval between R waves
LO-HI, ratio of low-frequency band to high-frequency band spectral power

CCHS is an extremely rare condition characterized by dysfunction of central respiratory control (1). Patients with CCHS have chronic respiratory insufficiency in the absence of primary pulmonary, cardiac, neuromuscular, or chest wall disease. Significant differences in the severity of ventilatory control exist among patients, ranging from those who require mechanical ventilation only during sleep to those in whom continuous ventilatory support is mandatory. An abnormal central integration of chemoreceptor neural input has been postulated as the mechanism responsible for the failure of autonomic control of ventilation in these children (1–5). No radiologic or pathologic evidence of specific brainstem or central nervous lesions reported to date could account for the unique clinical manifestations of CCHS (6). However, abnormal peak and interpeak latencies in brainstem auditory evoked responses, found in four diagnosed infants, imply a functional disturbance in brainstem control of ventilation (7).

CCHS may be associated with other conditions such as Hirschsprung's disease, neuroblastoma, and ganglioneuromas (4, 8–14). A primary defect of brain stem serotonergic nerve cell or a neural crest migrational abnormality has been suggested as a possible explanation for this linkage (9, 11, 13, 15). Indeed, neuroblasts from the neural crest migrate to form sympathetic ganglia, visceral autonomic ganglia, the chromaffin system, and other CNS structures. Although CCHS is associated with other neural crest congenital anomalies, the assessment of autonomic nervous system functions by measures such as HRV has not been systematically studied (4). Of current measures of autonomic nervous system function, HRV (the moment-to-moment change in heart beat intervals) provides a simple, noninvasive means of examining both short- and long-term patterns during different behavioral states. The loss of HRV is reported to reflect an alteration in autonomic nervous system function (16–18). A number of disease states are associated with changes in HRV, including heart failure (19, 20), sudden infant death syndrome (21), myocardial infarction (22, 23), prematurity (24), neonatal respiratory distress syndrome (25–28), and diabetes (29). We hypothesize that CCHS patients will exhibit changes in HRV and that these changes have the potential to provide insights into the nature of autonomic control in CCHS.

MATERIALS AND METHODS

Twelve subjects with CCHS and 12 healthy age- and sex-matched controls were studied from March to June 1991. Inclusion criteria for CCHS subjects were as follows: *1*) persistent evidence of sleep hypoventilation (arterial CO_2 pressure > 60 torr); *2*) onset of symptoms within the first year of life; *3*) absence of primary pulmonary disease or neuromuscular dysfunction that could explain the hypoventilation; *4*) no evidence of cardiac disease; and *5*) no medications that are known to alter HRV. Mean age was 5.85 y ± 4.3 SD (range 9 mo to 13 y). Other

Received July 11, 1991; accepted October 14, 1991.
Correspondence and reprint requests: Marlyn S. Woo, M.D., Division of Neonatology and Pediatric Pulmonology, Mailstop #83, Childrens Hospital of Los Angeles, 4650 Sunset Blvd., P.O. Box 54700, Los Angeles, CA 90054-0700.
Supported in part by grants from the National Institute of Child Health and Human Development (1 RO1 HD22696-01A1); the National Center for the Prevention of Sudden Infant Death Syndrome (Baltimore, MD); the Greater Los Angeles and Washington State Chapters of the National Sudden Infant Death Foundation; the Los Angeles County, Orange County, Inland Empire, and Kern County Chapters of the Guild for Infant Survival; the Junior Women's Club of Orange; and the Ruth and Vernon Taylor Foundation. M. A. W. is the recipient of the Audrienne Moseley Fellowship (UCLA School of Nursing). D.G. is the recipient of an American Physician Fellowship for Medicine in Israel, Inc.

demographic and relevant clinical information for CCHS subjects is noted in Table 1. CCHS patients and controls were enrolled in the study after informed consent was obtained (Children's Hospital of Los Angeles Institutional Review Board) from guardians and, whenever possible, from the patients themselves.

Twenty-four-h ambulatory Holter recordings were obtained from each subject in their home environment (Del Mar Holter models 456A and 459; Del Mar Avionics, Irvine, CA). Subjects were allowed to participate in their normal activities while wearing the recorder, and the subjects or their care givers maintained a diary of behavior, including sleep and waking times. During the study, all CCHS subjects received during sleep their routine mechanical ventilation, which was designed to achieve a P_{CO_2} of 30–35 torr (4–5 kPa). Holter tapes were scanned on a Del Mar 750 scanner (Del Mar Avionics), using semiautomatic scanning technique. Data obtained from the tapes provided the following information: time of beat, type of beat (sinus *versus* other), serial R-R intervals with a resolution of ±2.4 ms, R-R interval histograms, and SD of normal R-R intervals in 5-min epochs for the 24-h recording period.

HRV is constantly changing as a result of hemodynamic, neural, and hormonal perturbations. Previous researchers have studied these changes in HRV using spectral analysis. It has been suggested that the low-frequency spectral band reflects sympathetic tone, whereas high-frequency spectra may be associated with parasympathetic activity (30–32). We used spectral techniques as one of the measures of HRV in CCHS patients. We calculated spectral estimates on 256-beat epochs of interpolated heart rate using the fast Fourier transform. Two epochs were sampled, one during wakefulness at the time of highest heart rate in the recording and the other at the lowest heart rate during sleep. In addition, we examined six epochs at standard time periods of the day (0100, 0300, 0700, 0900, 1500, and 1700 h) in each subject. Two frequency bands of interest were defined: low frequency (0.04–0.12 Hz) and high frequency (0.224–0.28 Hz); then the LO-HI ratio was calculated (32). The high-frequency bands encompass the variation normally contributed by regular breathing, whereas the lower frequency components most likely derive from baroreceptor, temperature, and movement sources (31–33). SD and spectral analysis were obtained using the Del Mar Avionics Heart Rate Variability Analysis Program.

To assess instantaneous variation at different heart rates, we constructed Poincaré plots of each R-R interval plotted against the next interval (RR_n *versus* RR_{n+1}), using custom-designed software (Fig. 1) (19, 34). Poincaré plots simultaneously display overall variance, variance of dispersion of R-R intervals at each heart rate, and the change in variance as cardiac rate changes (34). Only sinus beats were used to generate the Poincaré plots, and all ectopic beats and sinus beats immediately before and after ectopic beats were removed. Poincaré plots were categorized into different patterns by seven physicians blinded to the patients' identification and diagnoses.

Heart rate and SD of HRV were compared between groups with unpaired t test. The χ^2 test was used for analysis of pattern distribution of Poincaré plot data and LO-HI ratios. Statistical significance was set at a p value <0.05.

RESULTS

Mean heart rates were not significantly different between the CCHS subjects (103.3 ± 17.7 SD beats/min) and controls (98.8 ± 21.6 SD beats/min; $t = 0.6$; $p > 0.5$, NS). Similar heart rate trends were observed in the 24-h recording period in all subjects (Fig. 2); *i.e.* heart rates tended to be higher during wakefulness and lower during sleep. SD of R-R intervals were not significantly different in CCHS subjects as compared with controls (102.2 ± 36.0 SD ms and 126.1 ± 43.3 SD ms; $t = -1.6$; $p > 0.1$, NS). Histograms of R-R intervals showed a bimodal distribution in 10 out of 12 CCHS subjects and six out of 12 control subjects ($\chi^2 = 3.0$; $p > 0.05$, NS) (Fig 3). In normal subjects, increased power in the high-frequency spectra occurred during quiet sleep compared with wakefulness, an observation not found in any CCHS patients ($\chi^2 = 24.0$; $p < 0.000001$). CCHS patients showed virtually no high-frequency activity during sleep (Fig. 4).

The LO-HI ratio increased in all but one CCHS subject during sleep compared with wakefulness and returned to wakefulness values upon arousal (Fig. 5). In contrast, the LO-HI ratio de-

Table 1. *CCHS patient information*

Age	Sex	Medications	Time on ventilator	Modality*
9 mo	Female	None	Sleep only	PP
10 mo	Male	None	Sleep only	PP
2 y	Female	Carbamazepine Albuterol	Sleep only	PP
2 y	Male	None	Sleep only	PP
2 y	Male	Ranitidine Cholestyramine Loperamide Albuterol	24 h	PP
5 y	Female	Phenobarbital Triamterene KCl Chlorothiazide Theophylline Albuterol	24 h (daytime = DP; nighttime = PP)	DP, PP
8 y	Female	Albuterol	Sleep only	PP
8 y	Male	Furosemide	24 h (3 h = DP; 21 h = PP)	DP, PP
9 y	Male	Furosemide Chlorothiazide KCl Phenobarbital Amiloride Albuterol	24 h (daytime = DP; nighttime = PP)	DP, PP
9 y	Female	Carbamazepine	Sleep only	NP
10 y	Male	Albuterol	Sleep only	PP
13 y	Male	Albuterol	Sleep only	PP

* DP, diaphragm pacing; NP, negative pressure; and PP, positive pressure.

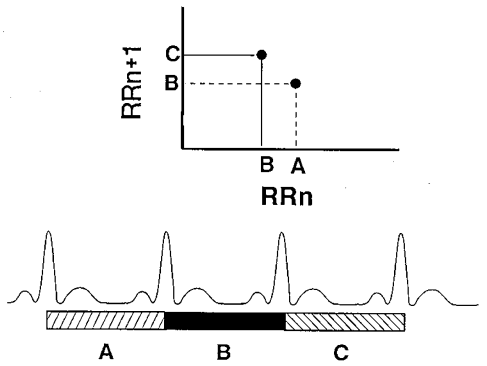

Fig. 1. Construction of Poincaré plot. *A*, *B*, and *C* represent consecutive R-R intervals. The first point is created using the *A* interval as the *x* coordinate and interval *B* as the *y* coordinate. The second point uses the *B* interval as the *x* coordinate and *C* interval as the *y* coordinate. The remaining points are constructed using each interval in turn as first the *x* coordinate and then, in the next point, as the *y* coordinate.

creased in all control subjects during sleep ($\chi^2 = 20.31$; $p < 0.000007$).

Poincaré plots of CCHS patients consistently differ from those of their controls (Fig. 6) ($\chi^2 = 24.0$; $p < 0.000001$). The Poincaré patterns of CCHS patients were correctly categorized by seven physicians who were unaware of the nature of the diagnosis (100% agreement). The extent of dispersion at decreasing heart rates (increasing R-R intervals) was diminished in all CCHS patient plots. The overall range of variation, expressed as the length of the cluster of points along the *x* axis, did not differ between individuals in each group (Fig. 6).

DISCUSSION

HRV in CCHS is different from that in controls on measures of Poincaré plots and aspects of spectral analysis. Poincaré plots in CCHS subjects were associated with minimal dispersion of R-R intervals as the heart rate slowed, *i.e.* as the R-R intervals lengthened (Fig. 6). Particularly striking was the uniformity of the CCHS Poincaré plot pattern across patients. Thus, the extent of variation at longer heart rate intervals is reduced in CCHS patients.

The LO-HI ratios in most CCHS patients increased during sleep but decreased in controls (Fig. 5). This suggests that an imbalance in sympathetic/parasympathetic activity is present in CCHS patients during sleep.

Spectral analysis revealed that sleeping CCHS subjects had more spectral energy in the low-frequency band, whereas the spectral analysis for sleeping controls showed a predominance of high-frequency activity. We suspect that respiratory sources contributed to the high-frequency peaks because these were at the respiratory frequency band of the spectra. We took particular care in sampling epochs for spectral analysis at the nadir of heart

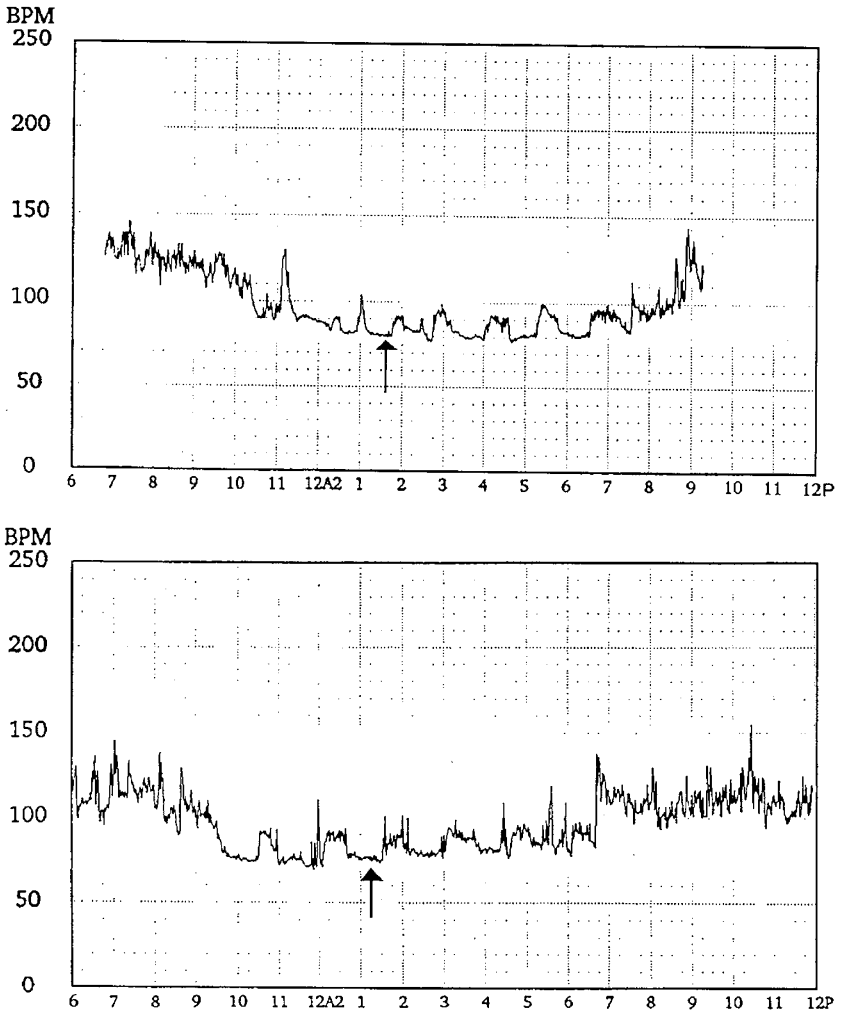

Fig. 2. Heart rate trends. The graphs of heart rate over the recording period. The *arrows* indicate the periods of lowest heart rate used for spectral analysis during sleep. The *top panel* represents the heart rate trend for a 5-y-old female with CCHS. The *bottom panel* is from a 5-y-old female control.

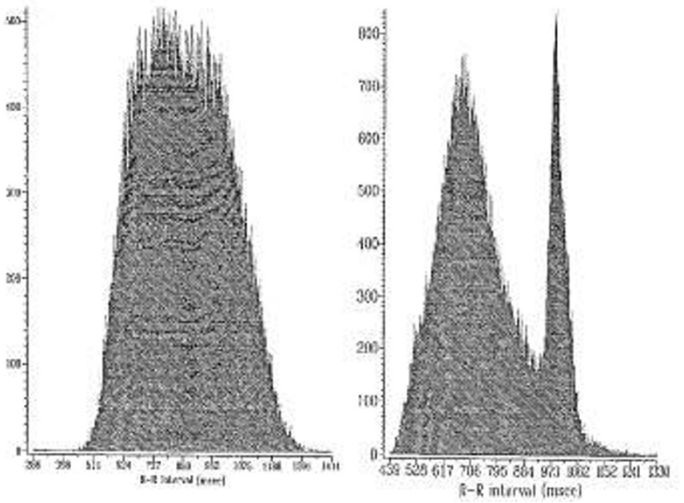

Fig. 3. R-R interval histograms. The *left panel* represents a unimodal distribution. The *right panel* is an example of a bimodal histogram.

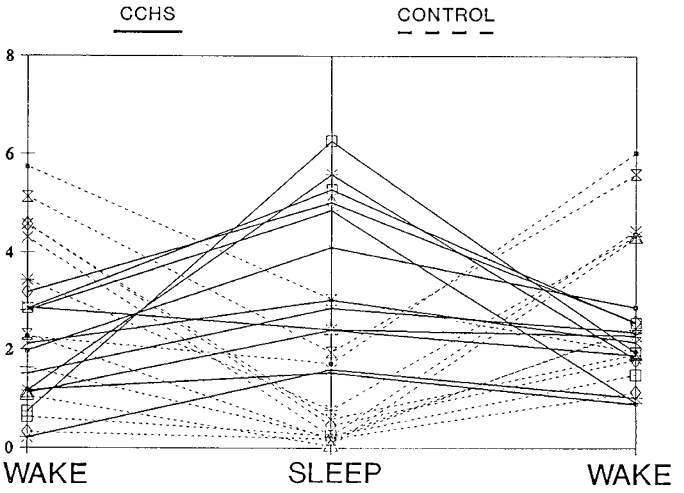

Fig. 5. LO-HI during wakefulness and sleep. LO-HI ratios during wakefulness and sleep in 12 CCHS patients and 12 age- and sex-matched controls.

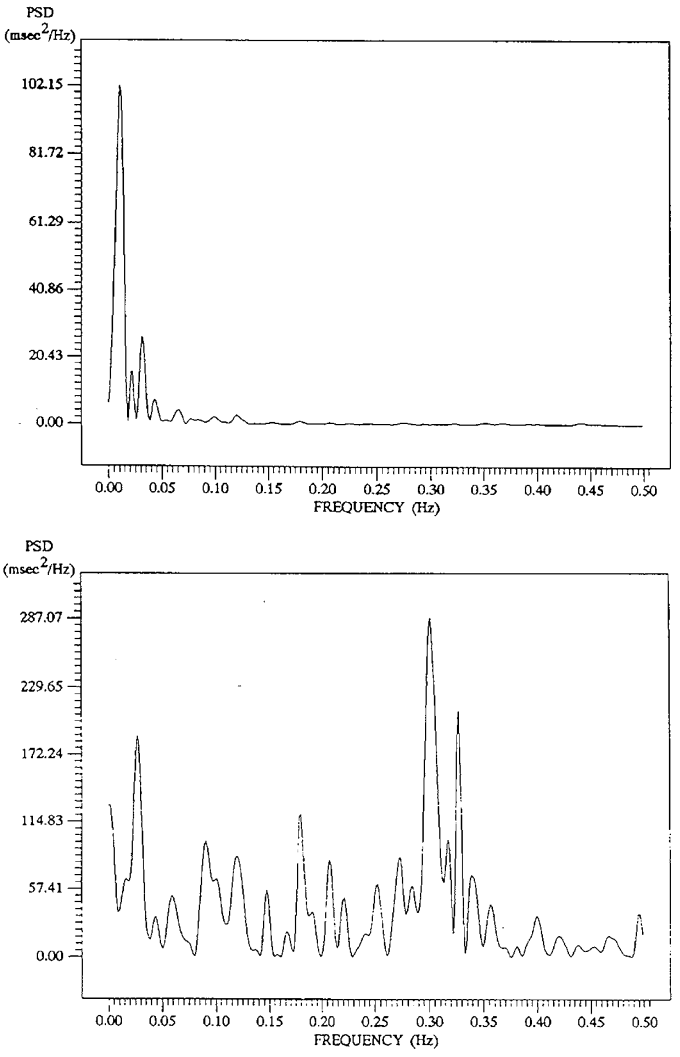

Fig. 4. Power spectral analysis during sleep. *Top panel* represents spectral analysis of R-R intervals during lowest heart rate periods in a 5-y-old female with CCHS. The *bottom panel* is from a 5-y-old female control.

rate during sleep, assuming that these epochs would represent similar behavioral states. Therefore, the observed differences do not reflect dissimilarity in sampling, but represent altered cardiac control in CCHS patients while they were asleep.

Several possible explanations for these differences in HRV may be advanced. A difference in circadian rhythm might contribute to these findings. However, circadian rhythm seems an unlikely cause, inasmuch as all subjects were exposed to the same light/darkness regimen and there was no evidence of endocrine disorders. Indeed, visual inspection of 24-h cardiac rate plots showed markedly similar troughs in heart rate during the night, suggestive of similar circadian influence on cardiac rate in both groups (Fig. 2).

Positive pressure ventilation might contribute to different patterns during nighttime in CCHS patients. Such mechanical ventilation causes intrathoracic pressure changes different from that which occurs in spontaneous breathing. These patients were intentionally hyperventilated [P_{CO_2} 30–35 torr (4–5 kPa)], thus suppressing spontaneous respiratory effort. The resultant hemodynamic changes alter baroreceptor reflexes, thereby modifying autonomic nervous system response. Poincaré plots and spectral analyses were similar for all CCHS subjects, even though assisted ventilatory techniques differed. Most CCHS patients used positive pressure ventilation only during sleep, but some patients were on continuous (24 h/d) mechanical ventilatory support and one patient used negative pressure ventilation at night (Table 1). Therefore, the technique of assisted ventilation would not likely explain the differences observed. However, all CCHS patients were ventilated using a fixed rate in control mode, and this fixed respiratory rate may be a factor in the decreased HRV observed in CCHS patients during sleep in this study.

Neurophysiologic mechanisms operating during sleep affect spectral LO-HI ratio differences. Among these mechanisms, altered excitatory influences from rostral and midbrain structures may differentially affect sympathetic outflow. During sleep, an increase in parasympathetic tone (suggested to be associated with high-frequency spectra) is expected and would thereby result in a decrease of the LO-HI ratio as seen in our controls. However, in the CCHS subjects, the nature of the variation (slow modulation of heart rate) suggests a substantial contribution from sympathetic sources during sleep. By selecting epochs from the lowest heart rate period during sleep, we can conclude that this variation did not originate from contributions of rapid eye movement sleep.

It appears from the Poincaré and spectral plots that sleep in CCHS is associated with preferential sympathetic contributions to heart rate variation. We speculate that a disturbance of inte-

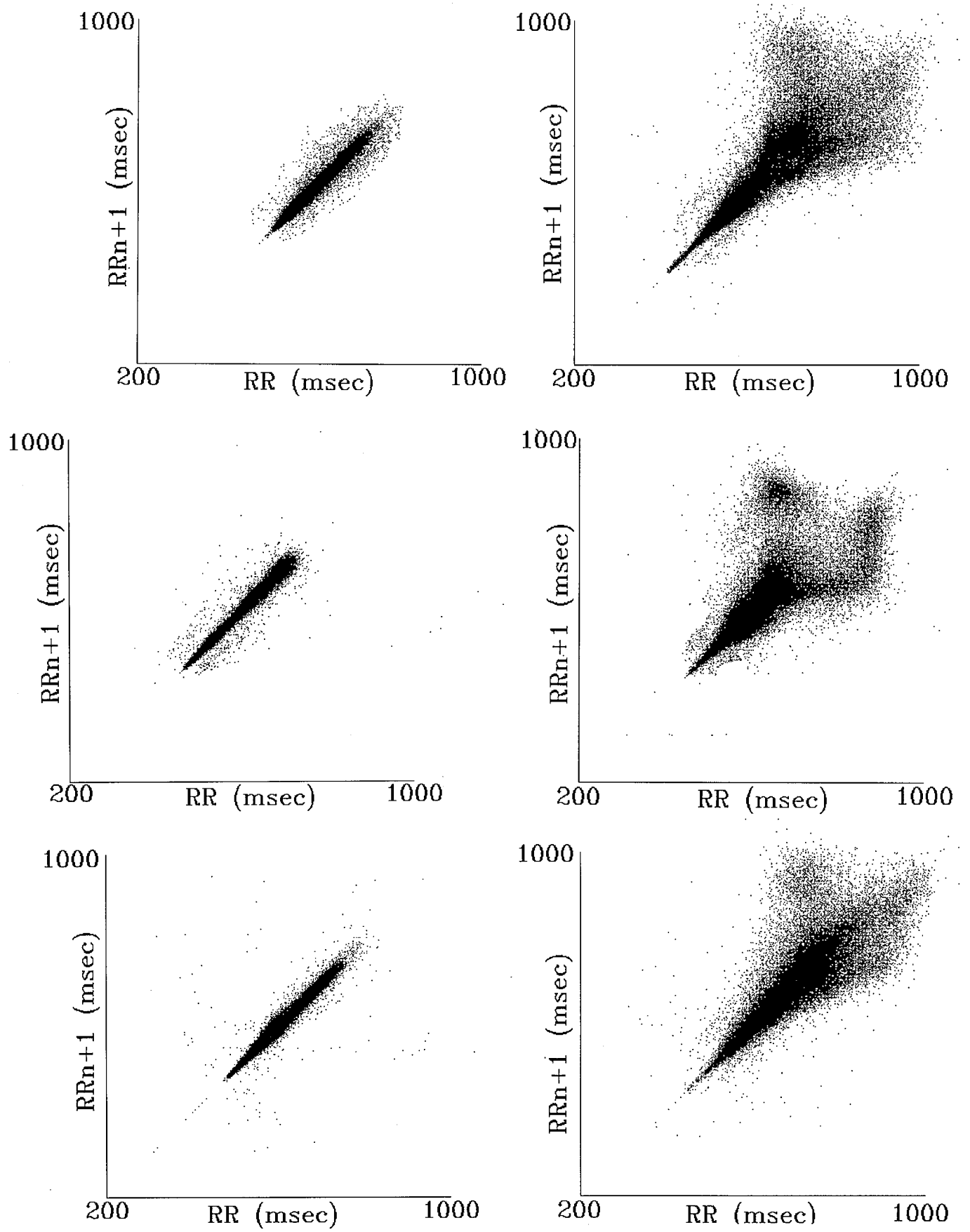

Fig. 6. Poincaré plots. Plots on the left are of CCHS subjects. Plots on the right represent age and sex-matched controls. *Top left panel* is from an 8-y-old male with CCHS. *Middle panel* is from a 5-y-old female with CCHS. *Bottom left panel* is from a 9-y-old female with CCHS.

gration of sympathetic tone may occur in CCHS patients. We have previously shown that the majority of CCHS subjects arouse to hypercapnic challenges during sleep despite absent hypercapnic ventilatory responses, a finding that suggests abnormal central integration of chemoreceptor input rather than absent or abnormal chemoreceptor function (35).

In summary, we have shown that the patterning of HRV is changed in CCHS. These changes suggest that, in addition to the loss of central ventilatory control, a disruption of autonomic regulation of the heart occurs.

Acknowledgements. The authors thank Daisy Bautista, Del Mar Avionics, and the UCLA Holter Lab for their assistance.

REFERENCES

1. Mellins RB, Balfour Jr HH, Turino GM, Winters RW 1970 Failure of automatic control of ventilation (Ondine's Curse). Report of an infant born with this syndrome and review of the literature. Medicine 49:487–504
2. Paton JY, Swaminathan S, Sargent CW, Keens TG 1989 Hypoxic and hypercapnic ventilatory responses in awake children with congenital central hypoventilation syndrome. Am Rev Respir Dis 140:368–372
3. Liu HM, Loew JM, Hunt CE 1978 Congenital central hypoventilation syndrome: a pathological study of the neuromuscular system. Neurology 28: 1013–1019
4. Haddad GG, Mazza NM, Defendini R, Blanc WA, Driscoll JM, Epstein AF, Epstein RA, Mellins RB 1978 Congenital failure of autonomic control of ventilation, gastrointestinal motility and heart rate. Medicine 57:517–526
5. Shannon DC, Marsland DW, Gould JB, Callahan B, Todres ID, Dennis J 1976 Central hypoventilation during quiet sleep in two infants. Pediatrics 57: 342–346
6. Weese-Mayer DE, Brouillette RT, Naidich TP, McLone DG, Hunt CE 1988 Magnetic resonance imaging and computerized tomography in central hypoventilation. Am Rev Respir Dis 137:393–398
7. Beckerman R, Meltzer J, Sola A, Dunn D, Wegmann M 1986 Brain-stem auditory response in Ondine's Syndrome. Arch Neurol 43:698–701
8. Guilleminault C, McQuitty J, Ariagno RL, Challamel MJ, Korobkin R, McClead RE 1982 Congenital central alveolar hypoventilation syndrome in six infants. Pediatrics 70:684–694
9. Hamilton J, Bodurtha JN 1989 Congenital central hypoventilation syndrome and Hirschsprung's disease in half sibs. J Med Genet 26:272–279
10. Stern M, Erttmann R, Hellwege HH, Kuhn N 1980 Total aganglionosis of the colon and Ondine's Curse. Lancet 1:877–878
11. Roshkow JE, Haller JO, Berdon WE, Sane SM 1988 Hirschsprung's disease, Ondine's Curse, and neuroblastoma-manifestations of neurocristopathy. Pediatr Radiol 19:45–49
12. O'Dell K, Staren E, Bassuk A 1987 Total colonic aganglionosis (Zuelzer-Wilson syndrome) and congenital failure of automatic control of ventilation (Ondine's Curse). J Pediatr Surg 11:1019–1020
13. Swaminathan S, Gilsanz V, Atkinson J, Keens TG 1989 Congenital central hypoventilation syndrome associated with multiple ganglioneuromas. Chest 96:423–424
14. Hunt CE, Matalon SV, Thompson TR, Demuth S, Loew JM, Liu HM, Mastri A, Burke B 1978 Central hypoventilation syndrome. Experience with bilateral phrenic nerve pacing in 3 neonates. Am Rev Respir Dis 118:23–28
15. Alvord Jr EC, Shaw CM 1989 Congenital difficulties with swallowing and breathing associated with maternal polyhydramnios: neurocristopathy or medullary infarction? J Child Neurol 4:299–306
16. Dalton KJ, Dawes GS, Patrick JE 1983 The autonomic nervous system and fetal heart rate variability. Am J Obstet Gynecol 146:456–462
17. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A 1986 Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 59:178–193
18. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzki LM, Steinman RC, Miller JP, the Multicenter Post-Infarction Research Group 1988 Components of heart rate variability measured during healing of acute myocardial infarction. Am J Cardiol 61:208–215
19. Woo MA, Stevenson WG, Moser DK, Harper RM, Garfinkel A, Trelease R 1990 Patterns of heart rate variability in heart failure. Circulation 82(suppl 3):III-709(abstr)
20. Casolo G, Balli E, Taddei T, Amuhasi J, Gori C 1989 Decreased spontaneous heart rate variability in congestive heart failure. Am J Cardiol 64: 1162–1167
21. Leistner HL, Haddad GG, Epstein RA, Lai TL, Epstein MAF, Mellins RB 1980 Heart rate and heart rate variability during sleep in aborted sudden infant death syndrome. J Pediatr 97:51–55
22. Kleiger RE, Miller JP, Bigger JT, Moss AJ 1987 Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59:256–262
23. Lombardi F, Sandrone G, Pernpruner S, Sala R, Garimoldi M, Cerutti S, Baselli G, Pagani M, Malliani A 1987 Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. Am J Cardiol 60:1239–1245
24. Jenkins JG, Reid MM, McClure BG 1980 Study of heart rate variability in sick newborn infants. Acta Paediatr Scand 69:393–396
25. Kero P 1974 Heart rate variation in infants with the respiratory distress syndrome. Acta Paediatr Scand [Suppl] 250:1–70
26. Vallbona C, Desmond MM, Rudolph AJ, Papp LF, Franklin RR, Rush JB 1963 Cardiodynamic studies in the newborn. II. Regulation of the heart rate. Biol Neonate 5:159–199
27. Urbach JR, Phuvichit B, Zweizig H, Millican E, Carrington ER, Loveland M, Williams JM, Lambert RL, Duncan AM, Farrell SL, Simons PO, Spurgeon IL 1965 Instantaneous heart-rate patterns in newborn infants. Am J Obstet Gynecol 93:965–974
28. Rudolph AJ, Vallbona C, Desmond MM 1965 Cardiodynamic studies in the newborn. III. Heart rate patterns in infants with idiopathic respiratory distress syndrome. Pediatrics 36:551–559
29. Bennett T, Farquhar IK, Hosking DJ, Hampton JR 1978 Assessment of methods for estimating autonomic nervous control of the heart in patients with diabetes mellitus. Diabetes 27:1167–1174
30. Saul JP 1990 Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. News Physiol Sci 5:32–37
31. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ 1981 Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 213:220–222
32. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H 1985 Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 17:H151–H153
33. Gordon D, Cohen RJ, Kelly D, Akselrod S, Shannon DC 1984 Sudden infant death syndrome: abnormalities in short term fluctuations in heart rate and respiratory activity. Pediatr Res 18:921–926
34. Raetz SL, Schechtman VL, Wilson AJ, Southall DP, Harper RM 1991 Dynamic analysis of cardiac R-R intervals in normal infants and in infants who subsequently died of sudden infant death syndrome. Soc Neurosci 17:729(abstr)
35. Marcus CL, Bautista DB, Amihyia A, Davidson Ward SL, Keens TG 1991 Hypercapneic arousal responses in children with congenital central hypoventilation syndrome. Pediatrics 88:993–998