

Respiratory Sinus Arrhythmia in Patients With Prader-Willi Syndrome

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ABSTRACT

In this investigation, we sought to further test the hypothesis that parasympathetic deficiency exists among persons with Prader-Willi syndrome, by examining respiratory sinus arrhythmia. The study sample comprised two groups of patients: 14 subjects with Prader-Willi syndrome and 14 age- and sex-matched controls. Each subject's electrocardiogram was recorded in a quiet room and digitized by a personal computer during five 1-minute periods. RR intervals within each 1-minute period were converted to heart rate in 120 successive 0.5-second intervals. The resultant heart rate time series was converted to its underlying frequency composition by a fast Fourier transform and averaged across minutes. Respiratory sinus arrhythmia was defined as the variability in the time series over a frequency range (0.096 to 0.48 Hz) corresponding to a range of respiratory rates from six to 30 breaths/minute. Analysis revealed significantly less variability in the heart rates of subjects with Prader-Willi syndrome relative to age- and sex-matched controls (group $\times$ frequency bin: $F = 2.26$, $P < .05$). An analysis of covariance adjusting for body mass index differences between the groups produced identical results. These findings support the existence of a parasympathetic deficiency among subjects with Prader-Willi syndrome independent of their body mass. This is likely due to dysregulation of the central autonomic network. (*J Child Neurol* 1996;11:121-125).

Prader-Willi syndrome is a genetically determined multi-system disorder with a prevalence of one in 10,000 to 15,000 individuals.¹⁻³ Hallmarks of Prader-Willi syndrome include central hypotonia, cognitive dysfunction, dysmorphic appearance, behavioral disturbances, hypothalamic hypogonadism, short stature, and obesity.¹⁻⁶ Many of the cardinal clinical features of Prader-Willi syndrome, eg, central hypotonia, hypothalamic disturbances, high pain threshold, and decreased salivation, have a neurologically based pathophysiology that involves both the central and peripheral nervous systems.⁷⁻¹² We have previously hypothesized that the underlying neurologic pathophysiology may in part be related to, or mediated by, the autonomic nervous system.¹³

Previous noninvasive studies of autonomic nervous system function have demonstrated primarily parasympathetic deficiency abnormalities in subjects with Prader-

Willi syndrome.¹³ Of particular note was the greater resting pulse rate, abnormal 30:15 RR interval ratio (the ratio calculated by dividing the RR interval in millimeters on the electrocardiogram at the 30th beat by that at the 15th beat after standing from supine rest), and pupil hypersensitivity to dilute parasympathomimetic drops (pilocarpine).

In this investigation, we sought to further test the hypothesis that parasympathetic deficiency exists among persons with Prader-Willi syndrome, by examining heart rate variability as it relates to respiratory sinus arrhythmia. There are vagal efferents to the heart that influence its rate relative to inspiratory depth and rate, so there is a parallel between overall vagal tone and heart rate variability. Respiratory sinus arrhythmia can be defined as the variability in heart rate (measured as power) over a frequency range of 0.096 to 0.48 Hz. This frequency corresponds to a range of respiratory rates from six to 30 breaths per minute and is sufficiently broad to encompass a wide range of interindividual and intraindividual peak respiratory rates. Respiratory sinus arrhythmia power spectra using frequency domain measures have been established as a purer measure of vagal tone than heart rate variability alone.¹⁴⁻¹⁶ The validity of respiratory sinus arrhythmia has been demonstrated by studying the effects of vagotomy and parasympathetic agonist and antagonist drugs.^{15,16} Under controlled experimental situations, there

Received Jan 30, 1995. Received revised May 3, 1995. Accepted for publication May 4, 1995.

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is a linear relationship between respiratory sinus arrhythmia and parasympathetic heart rate control.¹⁷ Debate exists, however, as to the validity of using respiratory sinus arrhythmia as a measure of pure parasympathetic tone, because parasympathetic efferents via vagal impulses to the heart are themselves intermittent and very brief.¹⁸ As a result, respiratory sinus arrhythmia as a measure of heart rate variability is perhaps better viewed as a measure of modulated parasympathetic activity.¹⁸

Respiratory sinus arrhythmia is mathematically derived from cardiac rate.¹⁴⁻¹⁶ Because normal resting heart rate is dependent on the individual's intrinsic cardiac heart rate and the net effect of cardio-excitatory (sympathetic) and cardio-inhibitory (parasympathetic) neural influences, any alteration in heart rate (sinus rhythm) necessarily reflects a change in their relative influence, net balance, or modulation. A major contributor to oscillation in resting heart rate is respiration. During exhalation, heart rate decreases slightly as parasympathetic influence increases. Conversely, during inhalation, there is a corresponding increase in the heart rate as parasympathetic influence decreases. This variability in heart rate or sinus rhythm exhibits fluctuations around the mean heart rate and is primarily controlled by involuntary adjustments of sinus rhythm by parasympathetic or cardio-inhibitory input mediated through the vagus nerve over a range of respiratory rates.^{15,16} By recording the fluctuations in sinus rhythm continuously, one can assess the degree of heart rate variability as a function of vagal modulation. This is accomplished by expressing heart rate in terms of its underlying frequency components and calculating the amount of variability within a frequency range that corresponds to the range of possible respiration rates. In the analysis of respiratory sinus arrhythmia, the band of heart rate frequencies of interest corresponds to a range of respiratory rates that includes the individual's peak respiratory rate.¹⁹ The resultant heart rate frequencies are converted to a power density score by spectral analysis. The power density scores obtained at each recording trial are summed and therefore represent heart rate variability associated with a range of respiratory rates. Although the relationship is not exact, experimental work has discerned that respiratory sinus arrhythmia is a better measure of cardiac vagal tone than simple heart rate variability.¹⁹

METHODS

Patients

Patients with Prader-Willi syndrome were recruited from the Prader-Willi syndrome clinic at the University of Connecticut Health Center. All subjects with Prader-Willi syndrome had a definitive diagnosis established by one of the authors (S.B.C.) using accepted clinical criteria and, in a majority of cases, supportive cytogenetic data.⁵ All patients with Prader-Willi syndrome were eligible.

Controls

Healthy age- and sex-matched volunteers from the Health Center served as controls.

Noninvasive Study

After informed consent was obtained, each subject was examined, and weight and height were measured. A body mass index was calculated using the formula: weight in kg/(height in m)². Each participant was evaluated while seated in a quiet laboratory room. Electrodes were placed on the skin and the electrocardiogram was recorded and digitized by an 80386 personal computer during five successive 1-minute intervals.

Analysis of Heart Rate Variability

The digitized electrographic data were recorded and analyzed during five successive 1-minute sampling periods. All RR intervals were measured and converted to heart rate divided into 120 successive, 0.5-second intervals. The resultant heart rate time series was ultimately converted into its underlying frequency composition by fast Fourier transform. Respiratory sinus arrhythmia was defined as the variability in heart rate (measured as power) over a frequency range of 0.096 to 0.48 Hz. This frequency corresponds to a range of respiratory rates from six to 30 breaths per minute and is sufficiently broad to encompass a wide range of interindividual and intraindividual peak respiratory rates.

Statistics

Spectral areas and standard deviations of RR intervals were compared between subjects with Prader-Willi syndrome and matched controls using Student's *t*-test. An analysis of variance was performed on data obtained to formally test the significance of differences found between subjects and controls. An analysis of covariance adjusting for age and body mass index was performed separately. A *P* value of less than .05 was considered significant.

RESULTS

Clinical Data

There were 28 individuals enrolled in the study: 14 subjects with Prader-Willi syndrome (six men and eight women) and 14 age- and sex-matched controls. The mean age was 30 years (range, 19 to 56 years) for subjects with Prader-Willi syndrome and 32 years (range, 17 to 51 years) for controls. There were no statistical differences between group mean ages. Five subjects with Prader-Willi syndrome were receiving medication at the time of study: four were taking fluoxetine (20 mg/day) and one was taking thioridazine (20 mg/day).

Heart Rate Variability Data

Figure 1 exemplifies the differences observed between subjects with Prader-Willi syndrome and controls. The upper panels demonstrate the variability in heart rate (*y* axis) over time in half-second intervals (*x* axis). The large peaks and valleys correspond to inhalations and exhalations, respectively. The lower panels represent the frequency spectra of heart rates. One can appreciate the obvious differences between these two study subjects: the subject with Prader-Willi syndrome (right) has smaller oscillations (power) in heart rate at a fairly uniform frequency (0.4 Hz). In the control subject (left), there are much larger oscillations (higher power) over a somewhat broader frequency range. Respiratory sinus arrhythmia is

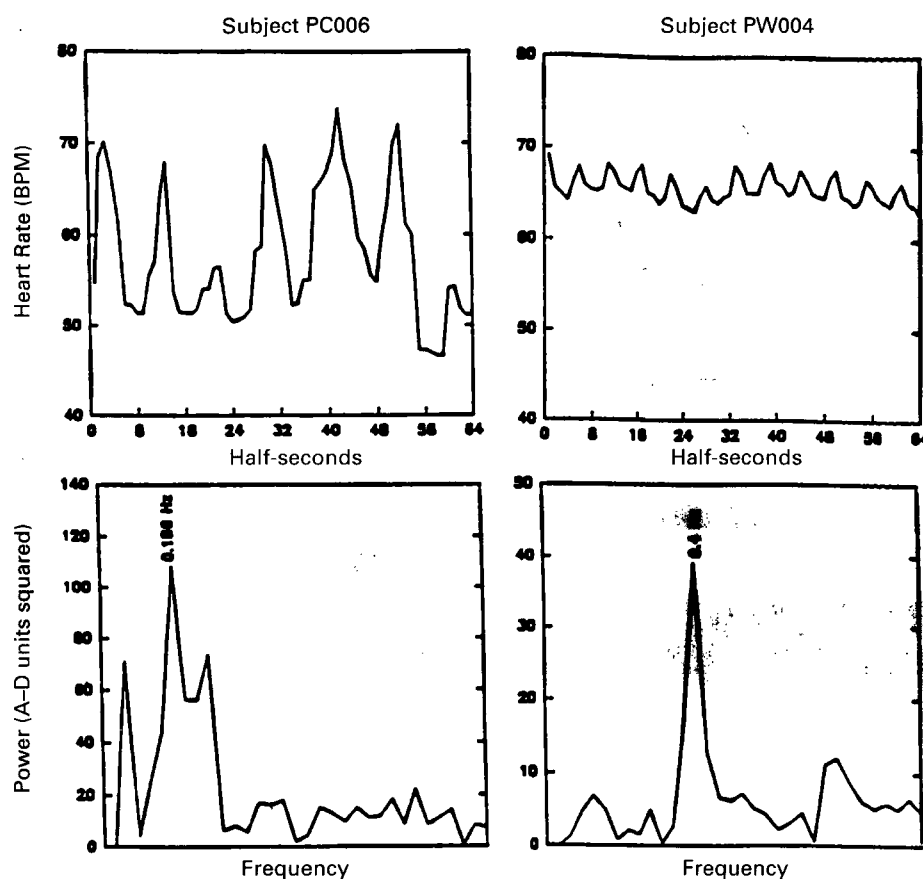


Figure 1. An example of one subject with Prader-Willi syndrome (right, upper and lower panels) and an age- and sex-matched control (left, upper and lower panels). The upper panels demonstrate the variability in heart rate (y axis) over time in half-second intervals (x axis). The large peaks and valleys correspond to the individuals' inhalations and exhalations, respectively. The lower panels are heart rates expressed by frequency composition. The high peaks are at 0.4 Hz in the subject with Prader-Willi syndrome and 0.186 Hz in the control subject.

estimated in these two subjects by the area under the curve from 0.1 to 0.5 Hz. These obvious differences remain when individual data are pooled within groups (Table 1).

Figure 2 is a composite of the mean frequencies of heart rate oscillations seen in each group. Subjects with Prader-Willi syndrome were found to have significantly less variability in heart rates in the respiratory sinus arrhythmia band than controls (group $\times$ frequency bin: $F = 2.26$, $P < .05$). When analysis was performed adjusting for body mass index, the results were the same, indicating that this decreased variability in heart rate occurs independently of body mass index.

DISCUSSION

Heart Rate Variability in Prader-Willi Syndrome

The measurement of respiratory sinus arrhythmia used in this study reflects the use of a standardized methodology now well accepted and commonly performed in the clinical assessment of autonomic system functioning. The decreased variability in heart rate that we observed in subjects with Prader-Willi syndrome provides additional data in support of our hypothesis that there is a reduced parasympathetic modulation of heart rate in these

patients. We further postulate that an underlying parasympathetic deficiency exists. Although there is an age-dependent variation in respiratory sinus arrhythmia, our age and sex matching, as well as covariance analysis, minimized any differences between subjects with Prader-Willi syndrome and controls. We emphasize, however, that the conclusions reached in this study pertain to sub-

Table 1. Raw Power Density Scores

Patient No.	Controls	PWS Subjects
1	15.94	41.32
2	57.70	20.41
3	80.01	21.86
4	20.13	22.07
5	28.03	28.21
6	56.35	59.08
7	33.31	25.22
8	29.19	93.47
9	32.36	5.35
10	15.54	27.62
11	73.18	9.27
12	30.64	25.23
13	—	23.04
14	—	17.72
Mean $\pm$ SD	34.32 $\pm$ 7.04	22.25 $\pm$ 3.88

PWS = Prader-Willi syndrome; SD = standard deviation.

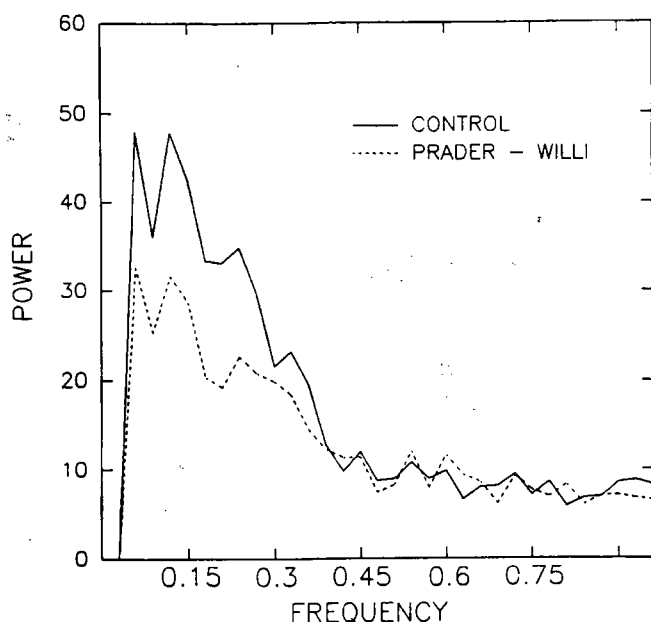


Figure 2. Group averages of the frequency range (in Hz) of resting heart rate. Solid line = control subjects; dashed line = subjects with Prader-Willi syndrome.

jects with Prader-Willi syndrome studied during wakefulness and cannot be extrapolated to various sleep states.

Physical conditioning has been shown *not* to correlate to respiratory sinus arrhythmia, whereas "poorer general clinical health" has been suggested to correlate with a decreased respiratory sinus arrhythmia.²⁰ Several studies have suggested that in highly trained endurance athletes, there is an acquired increase in parasympathetic activity, as measured by heart rate variability using respiratory sinus arrhythmia, compared to healthy nontrained controls.²¹⁻²³ However, lower resting heart rates in highly trained endurance athletes cannot be attributed to an increase in parasympathetic activity but rather is due to a reduction in intrinsic cardiac rate.²⁴ Control subjects studied in this investigation were not involved in aerobic, high-endurance physical training and, therefore, would not be expected to exhibit an increased parasympathetic activity state as reflected in higher heart rate variability via respiratory sinus arrhythmia. The body mass index has not previously been correlated with respiratory sinus arrhythmia, and we found no influence of body mass index on respiratory sinus arrhythmia in our analysis. Recent work has demonstrated a lack of correlation between body mass index, body weight, subcutaneous adipose tissue area, and angiographic severity of coronary disease.²⁵ Taken together, these findings suggest that the decreased variability in respiratory sinus arrhythmia is intrinsic to the study group (subjects with Prader-Willi syndrome) and not due to their physical conditioning or degree of obesity. The specificity of these results needs to be examined by using other control populations. Nonetheless, these observations are consistent with the findings of autonomic dysfunction we observed and presented earlier.¹³ In total, these results imply a relative imbalance or dysregulation in autonomic functioning that

could have an important role in the pathogenesis of the syndrome, as well as a potential avenue of therapy, especially because decreased respiratory sinus arrhythmia has been used as a predictor of increased risk of sudden cardiac death when combined with other factors.¹⁶

Comparison of the power spectral density curves between groups shows the largest divergence to be within the frequency range of 0.03 to 0.310 Hz. Our sampling methods (ie, serial 1-minute sample durations) do not allow resolution of the very low and low-frequency spectral peaks within the 0.002- to 0.2-Hz range. Other investigators have determined that spectra within this range correspond to thermoregulatory and vasomotor tone fluctuations (very low frequency range, 0.02 to 0.09 Hz), and baroreflex-related heart rate fluctuations (low frequency range, 0.04 to 0.13 Hz) under predominantly sympathetic influence, among other mechanisms.^{15,16,20,26} Future investigations will use longer sampling times to derive these specific spectral peaks and assess their corresponding regulatory mechanisms.

The results of this and our previous work support a possible role for central autonomic network dysfunction primarily disturbing parasympathetic regulation and function.^{13,27} Because the central autonomic network is made up of neurochemically complex circuitry with integrated reciprocal and parallel interconnections, it is difficult to specify an exact neuroanatomic site of an abnormality.²⁷ More aptly, faulty regulation of a centrally mediated autonomic reflex effect could provide the basis for a number of the recognized clinical disturbances in Prader-Willi syndrome noted to date.

The central autonomic network is made up of several nuclear regions and circuits that are well suited to serve as an anatomic model for the underlying pathogenesis of the syndrome. These include the prefrontal and insular cortices and amygdala, which could provide the substrate for personality and mood disturbances; the hypothalamic nuclei, which have been implicated in the concomitant endocrinopathy, faulty satiety, thermoregulatory, and sleep disturbances; the periaqueductal gray matter, involved in pupillary constriction, pain control, and stress-related aggression; the parabrachial pontine region, subserving reflex vomiting; nucleus tractus solitarius and nucleus ambiguus, which are viscerosensory relay stations; and the medullary intermediate reticular zone, involved in a host of respiratory, vasomotor, and cardiovagal regulatory functions.²⁷

We conclude the following: patients with Prader-Willi syndrome can be noninvasively examined for heart rate variability using analysis of respiratory sinus arrhythmia. Subjects with Prader-Willi syndrome were found to have decreased heart rate variability using respiratory sinus arrhythmia analysis. This decreased heart rate variability confirms the existence of decreased parasympathetic activity in subjects with Prader-Willi syndrome. We found no correlation between body mass index and the results of respiratory sinus arrhythmia analysis. The specificity and reliability of these findings will be evaluated in future studies.

Acknowledgments

This work was supported in part by grants from the Prader-Willi Syndrome Association and the Clinical Research Center at the University of Connecticut Health Center.

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