Power Spectral Analysis of Heart Rate Variability in Children and Adolescents With IDDM

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OBJECTIVE — To investigate power spectral analysis (PSA) of heart rate variability (HRV) in children and adolescents with IDDM, its relationship with other measures of HRV and standard cardiovascular responses, and factors associated with reduced HVR.

RESEARCH DESIGN AND METHODS — A total of 130 subjects with IDDM aged 12.8 ± 3.2 years and 108 healthy control subjects were studied. Power spectra were analyzed from supine electrocardiograph (ECG) recordings by processing into consecutive R-R intervals and analysis using fast Fourier transformation. Standard cardiovascular responses to deep breathing and standing were performed.

RESULTS — IDDM subjects had a reduction in total power including both low-frequency (0.05–0.14 Hz; $P = 0.0001$) and high-frequency (0.14–0.40 Hz; $P = 0.0002$) components. These changes were seen from diagnosis. Other measures of HRV, coefficient of variation (CV) and standard deviation (SD) of mean resting heart rate, were also significantly lower in IDDM. All 20 (15%) of the 130 IDDM subjects with total power less than the 5th percentile in control subjects also had reduced HRV when measured by CV of heart rate. There was an independent relationship between age and the high-frequency component in IDDM subjects and control subjects. Total power correlated with mean heart rate ($r = -0.56$; $P < 0.0001$), CV of heart rate ($r = 0.90$; $P < 0.00001$), SD of heart rate ($r = 0.91$; $P < 0.00001$), heart rate response to deep breathing ($r = 0.45$; $P < 0.0001$), and duration in IDDM subjects. There was no correlation with short-term or long-term metabolic control. Retesting of 27 subjects showed a variability in total power and its components comparable to other measures of HRV and standard heart rate responses.

CONCLUSIONS — Changes in HRV are a sensitive and reproducible measure of early autonomic dysfunction in childhood. In this age-group, PSA appears no more sensitive a measure of reduced HRV than other closely correlated measures of HRV.

Although symptomatic neuropathy is found rarely among young diabetic patients, subclinical changes on testing of nerve conduction (1), vibration sense (2), and cardiovascular reflexes (3) are well recognized. Some of the standard cardiovascular tests of autonomic function (4) have a limited role in children because of the need for patient cooperation and difficulties in performing adequate handgrip and Valsalva maneuvers (5).

Power spectral analysis (PSA) of heart rate variability (HRV) is now well established as a measure of sympathetic and vagal regulation of heart rate (6–9). The low- and high-frequency components of total spectral power are considered reciprocal indexes of sympathovagal and vagal interactions, respectively (9,10). It may provide a sensitive and acceptable measure of autonomic function in diabetes of short duration. However, there are limited pediatric data. Our aims were to compare PSA of HRV in children and adolescents with IDDM with control subjects, to relate PSA with other measures of HRV and standard tests of cardiovascular autonomic function, and to determine which factors are associated with abnormalities of HRV in this age-group.

RESEARCH DESIGN AND METHODS

Subjects

A total of 130 subjects with IDDM (aged 5.1–18.1 years) were randomly enrolled from the Diabetes Clinic of the Women's and Children's Hospital during a 4-month period (Table 1). Current HbA_{1c} was 8.1 ± 0.3% (mean ± SD); mean HbA_{1c} from diagnosis was 8.3 ± 0.2% (normal range 4–6%). Overnight albumin excretion ratio was 3.6 (1.2–27.1) (median [range]) μg/min. None of the patients had background retinopathy as determined on indirect fundoscopy performed by an ophthalmologist. Of these, 23 had been diagnosed for <1 year. Of the subjects, 27 were retested under identical conditions 2.9 ± 0.3 months later, and 108 healthy children (aged 8.0–17.9 years) enrolled from local metropolitan schools and were control subjects. Exclusion criteria for patients and control subjects were a history of cardiac or respiratory disease requiring medication, an intercurrent illness, or consumption of beverages or medications known to affect heart rate (e.g., caffeine-containing beverages) on the day of testing.

The study was approved by the human research ethics committee of the hospital, and informed written consent was obtained from parents and children >11 years.

Methods

A resting supine electrocardiograph (ECG) was obtained for 8–10 min using a Medtel HS 7 recorder (Medtel, Sydney, Australia). As the rate of respiration affected the high-frequency component of PSA, this rate was standardized for each subject at 18–22

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Abbreviations: CV, coefficient of variation; ECG, electrocardiograph; dBP, diastolic blood pressure; HR, heart rate; HF, high frequency; HRV, heart rate variability; LF, low frequency; PSA, power spectral analysis; sBP, systolic blood pressure.

Table 1—*Characteristics of IDDM and control subjects*

	n	M:F	Age (years)	Height (cm)	Weight (kg)	Duration IDDM (years)
IDDM subjects	130	74:56	12.8 ± 3.2	154.1 ± 16.2	52.4 ± 17.5	4.8 (1.9–7.7)
Control subjects	108	63:45	12.2 ± 2.8	152.3 ± 16.2	46.7 ± 16.0	
P value		NS	NS	NS	0.01	

Data are means ± SD or median (25th to 75th percentile).

breaths per minute using a run-in phase before ECG recording. The ECG output was processed into a tachogram of 512 consecutive R-R intervals on a Basic Time 386 DX-20 Computer using CVMS 1.2 data capture software (McPherson Scientific, Melbourne, Australia) and a CIO-AD 16 Jr analog-to-digital converter (Computer Boards, Mansfield, MA). The ECG recording was sampled at a rate of 1,000 Hz, giving an R-R interval accuracy of ±1 ms. Recordings were monitored in real time, and any artifacts were noted and edited before spectral analysis. However, only two artifacts of QRS complexes in total were noted owing to movement. No ectopic or morphologically abnormal QRS complexes were recorded in the study. R-R interval data were stored on computer and provided the basis for all subsequent PSA and standard cardiovascular response calculations. Mean R-R interval, mean resting heart rate (HR), and standard deviation (SD), and coefficient of variation (CV) of the mean resting HR were also calculated.

PSA was performed using the data processing module of the CVMS 1.2 software using fast Fourier transformation. Fast Fourier transformation was applied to R-R intervals sampled at 2 Hz and using Hanning ($\cos^2$) windowing with average subtraction normalization to minimize spectral leakage. For each subject, an average was obtained of 7 consecutive overlapped 128-point segments (512 sample points = 256 s) to minimize variance. The resulting power spectra have a resolution of 1/64 Hz expressed in units of milliseconds squared. The power spectra obtained were integrated over the following bands: *1*) low frequency (LF; 0.05–0.14 Hz), 2) high frequency (HF; 0.14–0.40 Hz), and 3) total power (0.05–0.40 Hz). In addition, the LF:HF ratio was derived.

Cardiovascular autonomic function was assessed by measuring standard cardiovascular responses to deep breathing and standing (11). Blood pressure was recorded using a Dinamap vital signs model 1846 SX/P automated blood pressure machine (Critikon, Tampa, FL). The blood pressure response to standing was calculated as the difference between 5 min supine and immediate standing systolic blood pressure (sBP) or diastolic blood pressure (dBP). The heart rate response to deep breathing was calculated using the mean difference between maximum and minimum heart rates during three cycles at 6 breaths per minute in the supine position. The heart rate response to standing (maximum:minimum ratio) was calculated as described by Ziegler et al. (12) with the longest R-R interval of beats 20–40 divided by the shortest R-R interval of beats 5–25.

Blood glucose measurements were performed on fingerprick samples with an Advantage glucose meter (Boehringer Mannheim, Sydney, Australia). HbA_{1c} was measured using a latex immunoagglutination-inhibition assay (DCA 2000 analyser, Bayer Diagnostics, Basingstoke, U.K.). This method shows close correlation with high-performance liquid chromatography (HPLC; $r = 0.97$; $n = 122$) (13). Interassay CV is 3.7–4.0%, and the mean HbA_{1c} was calculated for each IDDM subject using all previous measurements since diagnosis.

Statistical analysis

Statistical analysis was performed using Systat 5.03 software (Systat, Evanston, IL). Data that were not normally distributed (low- and high-frequency components, total power, LF:HF ratio, albumin excretion rate) were log-transformed (base 10) before analysis. Student's two-tailed *t* test was used for comparison of IDDM subjects and control subjects. Comparison of the number of subjects with abnormalities in different groups was performed using Yates' corrected χ^2 analysis. Stepwise multiple regression using a general linear model was used to assess the relationships of spectral power to disease variables and standard cardiovascular tests. Correlation coefficients were calculated using a Pearson matrix.

RESULTS — There was no sex difference in standard cardiovascular responses or PSA components.

Comparison of IDDM subjects and control subjects

IDDM subjects had a marked reduction in both LF and HF components of total power although the LF:HF ratio did not differ from control subjects (Fig. 1; Table 2), and significantly more IDDM subjects had total power and LF and HF values less than the 5th percentile of control subjects (Table 3). Other measures of HRV (CV and SD of mean resting HR) were also significantly lower in the IDDM subjects (Table 2), and significantly more IDDM subjects had CV of mean resting HR less than the 5th percentile of control subjects (Table 3). IDDM subjects had a higher sBP (resting and standing) than control subjects ($P < 0.001$, $P < 0.003$), with no significant difference in the BP response to standing. The IDDM group had a lower heart rate response to standing ($P = 0.01$) with more IDDM subjects having a response less than the 5th percentile for control subjects (Table 3). HR response to standing was weakly corre-

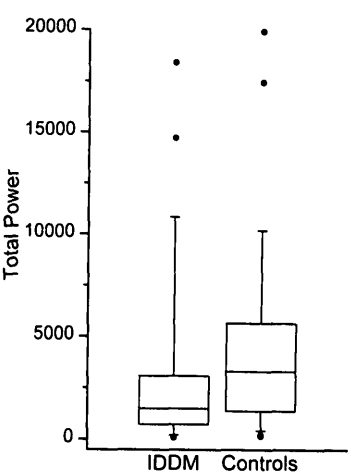

Figure 1—*Box and whisker plot showing distribution of total power in 130 IDDM subjects and 108 control subjects (P = 0.0001). The horizontal line represents the median, the limits of the box represent the 25th and 75th percentiles, the bar lines represent values within 1.5 × interquartile range, and outside values are shown.*

Table 2—*Standard cardiovascular responses and PSA in IDDM subjects and control subjects*

	IDDM subjects	Control subjects	*P*
n	130	108	
Mean HR	82.3 ± 11.9	79.2 ± 11.8	0.05
Resting BP (mmHg)			
Systolic	115 ± 10.7	109 ± 11.2	<0.0001
Diastolic	61.2 ± 7.8	60.2 ± 6.9	NS
BP response to standing (mmHg)			
Systolic	−3.5 ± 9.2	−2.6 ± 8.3	NS
Diastolic	−5.6 ± 6.3	−6.6 ± 6.5	NS
HR response to deep breathing (beats/min)	31.9 ± 8.6	33.7 ± 7.5	NS
HR response to standing (max/min ratio)	1.41 ± 0.24	1.49 ± 0.24	0.01
PSA of HRV			
$\log_{10}$ LF	2.79 ± 0.40	2.99 ± 0.38	0.0001
$\log_{10}$ HF	2.91 ± 0.59	3.18 ± 0.51	0.0002
$\log_{10}$ total power	3.18 ± 0.49	3.43 ± 0.43	0.0001
$\log_{10}$ LF:HF ratio	−0.12 ± 0.31	−0.19 ± 0.28	NS
CV of HR	7.95 ± 3.46	9.46 ± 3.35	0.0008
SD of HR	60.7 ± 31.1	73.9 ± 29.1	0.001

Data are mean ± SD or *n*.

lated to concomitant blood glucose levels (13.6 ± 6.4 mmol/l [mean ± SD], $r = -0.25$, $P = 0.004$).

The 23 recently diagnosed IDDM subjects with 1.2 (1.2–12.0) months (median [range]) duration were younger than the rest of the IDDM subjects (11.1 ± 3.1; 13.2 ± 3.1 years, $P = 0.004$). They did not differ in their total power (2,093 [1,235–3,112] vs. 1,320 [712–3,048] median [25th to 75th percentile]) or LF and HF components. Of the recently diagnosed IDDM subjects, 4 of the 23 (17%) had total power and LF and HF values below the 5th percentile of control subjects. The same four IDDM subjects also had CV of heart rate, SD of heart rate, and HR response to standing below the 5th percentile of control subjects and had a mean resting heart rate above the 95th percentile of control subjects.

Age effects

Multivariate analysis was performed in the IDDM group to clarify the respective contributions of age and duration of IDDM to PSA parameters. Analysis showed an independent correlation of the HF component ($r = -0.25$; $P = 0.004$) (Fig. 2) and LF:HF ratio ($r = 0.28$; $P = 0.001$) with age but not with duration of IDDM, but showed an independent correlation of both the LF component ($r = -0.20$; $P = 0.02$) and total power ($r = -0.22$; $P = 0.01$) with duration of IDDM (Figs. 3*A* and *B*). A correlation with age was also seen in the control population for both the HF component ($r = -0.27$; $P = 0.01$) and LF:HF ratio ($r = 0.42$; $P = 0.0001$).

We also analyzed the effect of age on standard cardiovascular responses. Our data showed a negative correlation in the IDDM group between age and sBP response to standing ($r = -0.29$; $P = 0.001$), as well as HR response to deep breathing ($r = -0.31$; $P = 0.0004$). These relationships were independent of duration of IDDM. A negative relationship between age and HR response to deep breathing ($r = -0.26$; $P = 0.008$) and standing ($r = -0.22$; $P = 0.03$) was seen in the control subjects.

Relationship between total spectral power and standard cardiovascular responses

There were strong and significant correlations in both IDDM and control groups between total spectral power and the heart rate response to deep breathing, as well as to the mean heart rate, after controlling for age. Weak correlates with other cardiovascular responses were regarded as clinically insignificant (Table 4). Total spectral power also correlated strongly with CV of heart rate in IDDM ($r = 0.90$; $P < 0.00001$) and control subjects ($r = 0.91$; $P < 0.00001$).

Relationship between total spectral power and other IDDM variables

We found no relationship between PSA components or other measures of HRV (CV of heart rate and SD of heart rate) and simultaneous blood glucose, current HbA_{1c}, mean HbA_{1c} from diagnosis, or overnight albumin excretion rate.

Biological variability

We retested 27 subjects with IDDM at a separate clinic visit 2.9 (2.0–3.2) months later and measured the ratio between the first and second tests of standard cardiovascular responses and PSA components. The CV for the PSA components was comparable to those of the standard heart rate cardiovascular responses and other measures of HRV (Table 5).

CONCLUSIONS — The study provides new information relating to power spectral analysis of HRV in children and

Table 3—*IDDM patients with abnormality of cardiovascular responses and HRV*

	IDDM subjects	Control subjects	*P*
n tested	130	108	—
Mean HR*	15	7	NS
HR response to deep breathing†	14	6	NS
HR response to standing†	22	6	0.01
PSA of HRV†			
$\log_{10}$ LF	19	6	0.04
$\log_{10}$ HF	19	6	0.04
$\log_{10}$ TP	20	6	0.03
CV of HR†	24	6	0.005
SD of HR†	17	6	NS

Data are *n*. *P* value for Yates' corrected χ^2 analysis. *n > 95th percentile of control subjects; †n < 5th percentile of control subjects.

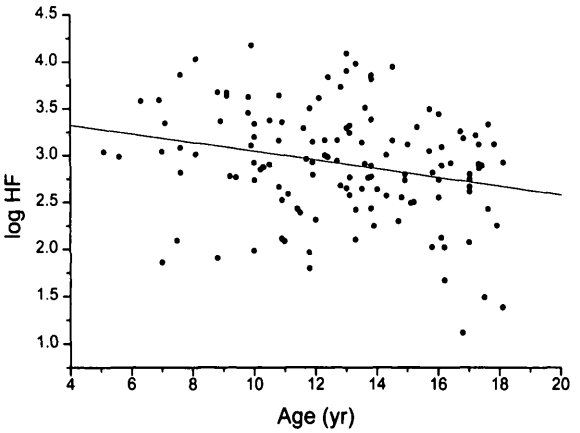

Figure 2—*The relationship between age and high-frequency component (r = −0.25, P = 0.004) in 130 IDDM subjects.*

adolescents with IDDM, its variability and relationship with other measures of HRV, standard cardiovascular responses, age, and duration. Our data show a reduction of total spectral power and its components in children with short duration of IDDM. These changes occurred from the 1st year after diagnosis, which is consistent with previous findings of early abnormalities of autonomic and peripheral nerve function in young adults (14–17).

PSA of HRV and other measures of HRV were generally more discriminatory than standard cardiovascular responses in comparing children with IDDM and control subjects. This suggests that changes in heart rate and its variability are one of the first and most sensitive signs of autonomic dysfunction in children with IDDM. It is noteworthy that the relatively simple measurement of HRV, CV of resting HR, appeared as sensitive a measure of HRV as PSA. Standard cardiovascular responses have been studied in children with IDDM for some years. Of them, heart rate responses to deep breathing and standing are considered the most discriminatory indicators of early changes in autonomic function with generally no consistent association with either metabolic control or duration at this early stage (18,19).

The low- and high-frequency components of total spectral power are considered reciprocal indexes of sympathovagal and vagal interactions, respectively (9). Considering the reduction in total spectral power, the ratio of low-frequency to high-frequency components did not alter in IDDM children. This has been shown also in adults with diabetic autonomic neuropathy (9). The decline in the high-frequency component of spectral power, but not the low-frequency component, with increasing age of both control subjects and IDDM subjects is explained by the decline in the contribution of respiratory sinus arrhythmia to the high-frequency component with increasing age. Sinus arrhythmia, which is the variation of heart rate in relation to respiratory activity, declines with increasing age in children and adolescents. It affects the high-frequency component because this component is dependent upon respiratory rate and vagal tone (10,20). This age-related phenomenon, whereby age has a major contribution to the high-frequency component, is the likely explanation of the independent effect of duration of IDDM on the low-frequency component and total power, but not on the high-frequency component of the spectrum. The age-related effects on standard cardiovascular responses have been shown previously (18,21). The correlation we found between concomitant blood glucose and heart rate response to standing was relatively weak and limited to this cardiovascular response. Concomitant blood glucose has been shown to affect gastric emptying (22) and peripheral nerve conduction velocity in IDDM (23), and in normal subjects there is a relationship between blood

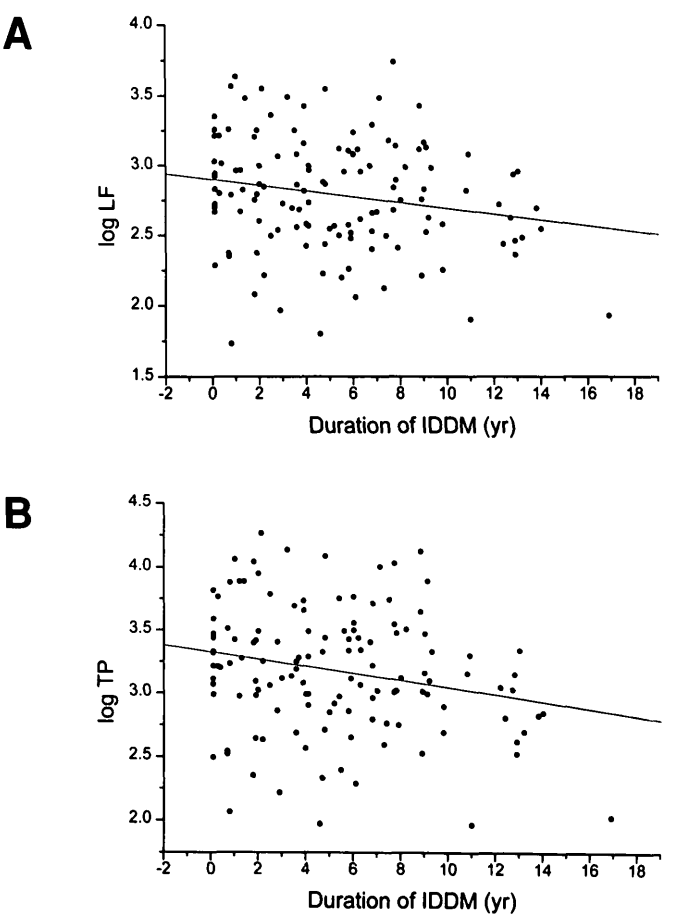

Figure 3—*The relationship between duration of IDDM and low-frequency component (r = −0.20, P = 0.02) (A) and total power (r = −0.22, P = 0.01) (B) in 130 IDDM subjects.*

Table 4—*Relationship between total spectral power and standard cardiovascular reponses in IDDM subjects and control subjects*

	IDDM subjects (n = 130)		Control subjects (n = 108)	
	r	P value	r	P value
Mean HR	−0.56	<0.0001	−0.57	<0.0001
HR response to deep breathing	0.45	<0.0001	0.35	<0.0001
HR response to standing	0.12	0.03	0.20	0.02
BP response to standing	NS		0.14	0.004

glucose and heart rate response to standing (24), as we have shown in IDDM.

The biological variation of HRV was similar whether determined by PSA, CV, or SD of mean heart rate, which in turn were of similar variability to standard heart rate responses. This provides the potential for HRV to be interpreted longitudinally in the assessment of autonomic function. At present, the long-term significance of these early subclinical changes of autonomic function is not known, as no prognostic relationship has been made with later clinical autonomic neuropathy.

HRV in adults with IDDM also reveals early changes before symptoms (25–27), and early changes in HRV have been associated with microalbuminuria (28). We found no relationship with albumin excretion rate, but few patients had microalbuminuria. The one previous study examining PSA of HRV in children examined patients of similar age and duration to our study (29). They found no independent effect of age on HRV in the diabetic patients, but their spectral analysis excluded much of the high-frequency component and thereby the contribution of respiratory sinus arrhythmia. They found a relationship with metabolic control particularly at higher HbA_{1c} levels. Our patients were relatively well controlled, and it is possible that this prevented a relationship with metabolic control being observed. Our study extends previous pediatric data by relating PSA of HRV to other measures of HRV and standard cardiovascular responses. We were able to examine variability in a group of IDDM subjects, which to our knowledge has not been addressed in this age-group.

We conclude that PSA and other measures of HRV are a sensitive and feasible means of assessing the first changes in autonomic function in children with IDDM. PSA appears to be no more sensitive a measure of reduced HRV than other measures of HRV. They are potentially useful tools to examine longitudinal changes and their relationship to long-term clinical autonomic neuropathy and other microvascular complications.

Table 5—*Variability of standard cardiovascular responses and PSA in IDDM subjects*

	Ratio test 2/test 1	CV
n	27	27
Mean HR	0.975 ± 0.106	0.108
Resting BP		
Systolic	1.037 ± 0.078	0.075
Diastolic	0.987 ± 0.107	0.109
BP response to standing		
Systolic	1.382 ± 1.141	0.826
Diastolic	1.674 ± 1.154	0.689
HR response to deep breathing	1.019 ± 0.244	0.240
HR response to standing	0.938 ± 0.133	0.142
PSA of HRV		
$\log_{10}$ LF	1.069 ± 0.135	0.126
$\log_{10}$ HF	1.105 ± 0.187	0.169
$\log_{10}$ total power	1.073 ± 0.122	0.114
CV of HR	1.150 ± 0.340	0.296
SD of HR	1.210 ± 0.444	0.366

Data are means ± SD.

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