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Heart Rate Variability in Diabetic Children: Sensitivity of the Time- and Frequency-Domain Methods

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SUMMARY. **Heart rate variability (HRV) is a noninvasive index of the neural activity of the heart. Although also influenced by the sympathetic activity of the heart, HRV is essentially determined by the vagal stimulation of the heart. Several HRV abnormalities have been described in adults with diabetes mellitus. However, there are few data on HRV in children with diabetes mellitus. In the present study, HRV was assessed in seven healthy children, 10 diabetic children with good glycemic control and 11 diabetic children with poor glycemic control. All had normal standard cardiac autonomic function tests, obtained from 24-h Holter tapes. HRV was measured by calculating six time-domain (mean R–R interval (RR), standard deviation of the R–R interval [SDRR], standard deviation of the mean of 288 R–R intervals [SDANN], the mean of the 288 standard deviations computed for each 5-min period [SD], percentage of differences of adjacent R–R intervals of >50 msec for the entire 24 h [pNN50], and the root mean square of successive differences [rMSSD]) and four frequency-domain (low frequency [LF], high frequency [HF], total heart rate power spectra, and LF/HF ratio) indexes. SD, pNN50, rMSSD, LF, HF and total heart rate power spectra were markedly and significantly reduced in diabetic children with poor metabolic control. The 24-h variation of low- and high-frequency components of heart rate power spectra of the latter children had a different shape. Thus, diabetic children with poor metabolic control (elevated HbA_1c and B_2M levels) have a low HRV compared to those diabetic children with good control and healthy children. These results can be interpreted as evidence of cardiac autonomic neuropathy in diabetic children with asymptomatic diabetic autonomic neuropathy.**

KEY WORDS: **Heart rate variability — Time-domain measurements — Frequency-domain measurements — Cardiac autonomic neuropathy — Diabetic children**

Diabetic autonomic neuropathy is a well-known complication of diabetes and contributes significantly to its morbidity and mortality [5, 17, 35, 36]. It is obvious that autonomic neuropathy is closely associated with glycemic control [35]. Autonomic neuropathy in diabetic subjects is gradual in its onset, with signs often hidden for many years by reflex compensatory mechanisms [5, 17, 35, 36]. Murray et al. [24] showed that the vagal neuropathy is apparent before any sympathetic damage. Since this process takes time, it is uncommon in young children with diabetes. Young et al. [35] reported a 31% incidence of parasympathetic neuropathy in teenage diabetics and suggested the association between this complication with poor glycemic control. Simple bedside tests of autonomic function in diabetes are widely available to diagnose autonomic neuropathy [17, 35, 36]. Since these tests have only been able to detect severe impairment of autonomic nervous system, it is necessary to determine the autonomic dysfunction before this period [4, 6, 7, 9, 14, 16, 18, 20, 22, 25, 29]. Tests of autonomic function also tend to classify patients merely on the basis of presence of neuropathy [17, 35, 36].

In many studies of circulatory physiology and clinical cardiology, analysis of heart rate variability (HRV) has been used a measure of cardiac auto-

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nomic function [1, 13, 19, 28, 32, 34]. The measurement of R–R interval variation as an autonomic test in diabetes has been carefully reviewed and fulfils many of the characteristics of an accurate practical test [5, 6, 24]. Ewing et al. [4] noted a reduction in 24-h HRV in diabetic subjects with normal cardiovascular reflexes to the lower end of the normal range.

In the past decade, a variety of indexes of HRV have been proposed. The indexes can be divided into two major categories: time-domain (nonspectral) and frequency-domain (spectral) analysis [4, 6, 19, 24, 28, 29, 32, 34]. Time-domain methods have been routinely used to assess cardiac autonomic function [4, 5, 6, 14, 24, 25, 29]. Frequency-domain measurements of HRV have been used recently [1, 28, 32, 34]. The actual correlations between each of the indexes have not been evaluated. The time- and frequency-domain measurements of HRV have been widely assessed in diabetic adults [4, 6, 7, 9, 14, 16, 18, 20, 22, 25, 29]. There are few reports in childhood diabetes [19, 24, 35, 36].

In this study, we examined the correlations of six time-domain and four frequency-domain indexes of HRV in diabetic children with good and poor glycemic control, and in healthy age-matched children. The aim of the present study was to determine the predictive value of these indexes in diabetic children with normal standard autonomic function tests. We also examined the actual correlations between these indexes and diabetic cardiac autonomic neuropathy.

Materials and Methods

Controls and Patients

Control group (group 1) involves seven healthy children. All of them had a normal medical history and physical examination. They had no evidence or history of chronic disease and were not on any medications. Their average age as well as glycosylated hemoglobin (HbA_1c) and β_2-microglobulin (β_2 M) levels are listed in Table 1, as are the corresponding data in children of group 2 (diabetics with good glycemic control) and group 3 (diabetics with poor glycemic control). All diabetic children have been treated with standard insulin injected subcutaneously.

Methods

Autonomic function tests. All subjects underwent several autonomic function tests. Detailed methods have been described before [8, 15]. The tests included the following; heart rate response to deep breathing, to standing (30 : 15 ratio), to the Valsalva maneuver, to carotid massage, and blood pressure response to standing [8, 15]. Patients were rated from 0–5, based on the number of abnormal tests.

Table 1. Age, glycosylated hemoglobin, β_2-microglobulin, and duration of diabetes in groups 1–3

	Group 1 (n = 7)	Group 2 (n = 10)	Group 3 (n = 11)
Age (year)	10.8 ± 3.5 (6–14)	11 ± 2.7 (9–18)	10 ± 2.8 (6–15)
Glycosylated hemoglobin (g/dl)	4.7 ± 1.4 (2.4–6.4)	6.1 ± 0.6 (5.3–7.1)	11.1 ± 1.4[a] (9–13.5)
β_2-Microglobulin (μg/L/24 h)	78.4 ± 17.5 (20–98.5)	96.5 ± 22.8 (16–108)	321 ± 68.6[a] (220–792)
Duration of diabetes (year)	—	4.1 ± 2.1 (3–10)	3.2 ± 1.2 (2–6)

Group 1, healthy age-matched children; group 2, diabetic children with good glycemic control; group 3, diabetic children with poor glycemia control.
[a] $p < 0.01$ compared group 3 with groups 1 and 2.

Holter monitoring. Continuous ambulatory ECG monitoring was performed using two-channel Marquette series 8000 Laser Holter SXP analysis system. The parents of children were advised to record sleeping, activities, etc.

Analysis of 24-h Holter recordings. All Holter tapes were analyzed with use of a Marquette 8000 scanner running version 5.8 of the Marquette analysis program to identify and label each QRS complex. After the computer had automatically detected and labeled each QRS complex, the data file was reviewed and edited by a physician. After editing, the labeled QRS data stream was moved by means of high-speed interface to a microcomputer, where the data were analyzed by a computer program and additional editing was done. Measures of heart period variability were calculated and printed for the entire 24 h. There had to be >18 h of analyzable data for the 24-h recording to be accepted for analysis. Each print-out, including ECG strips, was reviewed by a cardiologist to make sure that R–R intervals were correctly selected and measured.

Analysis of successive R–R (N–N) intervals. The mean R–R interval was computed by selecting only those coupling intervals that contained no ectopics or noise and did not exceed a user-specified longest R–R interval. The standard deviation of the mean R–R interval was computed as SDRR. The SDANN index is the standard deviation of the 288 mean R–R intervals, which are computed for all normal-normal coupling intervals within a 5-min period. SD is the mean of up to 288 standard deviations computed for each 5-min period. We computed the absolute value of each individual difference between adjacent R–R intervals and summarized the differences by the percentage of differences >50 ms for the entire 24 h (pNN50). The root mean square of successive differences (rMSSD) was calculated on R–R intervals with the formula of von Neumann et al. [33].

Power spectral analysis of R–R intervals. The average R–R interval was subtracted from the time series and Fast Fourier transforms were performed to resolve the frequency component. We computed heart period power spectra on each 2-min segment of each 24-h recording. A spectral plot for 1 h is the average of 30 spectra computed over 2-min periods. Only normal–normal intervals are used. In the process each interval excluded because

Table 2. Heart rate variability with time- and frequency-domain analysis in diabetic children and healthy age-matched children

	Group 1 (n = 7)	Group 2 (n = 10)	Group 3 (n = 11)
Time-domain analysis			
Mean RR (ms)	701 ± 54	726 ± 52	620 ± 75[a,b]
SDRR (ms)	166 ± 33	174 ± 52	117 ± 41[c]
SDANN (ms)	129 ± 18	150 ± 45	107 ± 37[d]
SD (ms)	76 ± 17	76 ± 21	43 ± 16[e]
rMSSD (ms)	76 ± 18	64 ± 19	31 ± 18[e]
pNN50 (%)	29 ± 7	28 ± 7	7.8 ± 8[e]
Frequency-domain analysis			
Total power (ms)	61.3 ± 16.7	57.3 ± 14.5	32.2 ± 12.4[e]
LF (ms)	34.7 ± 11.2	34 ± 8	20 ± 8[e]
HF (ms)	34.4 ± 10.2	30 ± 9	15 ± 8[e]
LF/HF	1 ± 0.08	1.2 ± 0.3	1.6 ± 0.6[f]

Group as defined in Table 1.
[a] $p < 0.01$: group 3 vs. group 2.
[b] $p < 0.05$: group 3 vs. group 1.
[c] $p < 0.05$: group 3 vs. groups 1 and 2.
[d] $p < 0.05$: group 3 vs. group 2.
[e] $p < 0.01$: group 3 vs. groups 1 and 2.
[f] $p < 0.01$: group 3 vs. group 1.

of ectopics or artifact was replaced by holding the previous coupling interval level throughout of the time interval to the next valid coupling interval. Spectral measures were computed as square root of areas under power spectrum. Square roots of variance (standard deviation) displayed familiar units of milliseconds. Frequency-bounded areas under the power spectrum represent signal variance within frequency bands. Two major peaks were identified in the spectrum: a low-frequency component centered around the 0.04–0.15 Hz, and a high-frequency peak centered around the respiratory frequency (usually 0.15–0.40 Hz). We also computed total power spectrum (0.01–1 Hz) and low-frequency/high-frequency ratio that is thought to reflect the net sympathetic contribution to HRV.

Statistical Analysis

Data are presented as means ± SEM. Differences between the groups have been tested with the analysis of variance (ANOVA). Differences were considered significant at $p < 0.05$.

Results

Age duration of diabetes in two groups with diabetes and in control group did not differ significantly ($p > 0.05$). However, HbA_1c and β_2 M levels in diabetic children with poor glycemic control were significantly higher than those in the other two groups ($p < 0.01$) (Table 1). Autonomic function tests in all groups were normal according to the described protocol.

Results displayed in Table 2 represent the analysis of HRV by time-domain and frequency-domain methods in 28 children which enrolled in the study.

Time-Domain Measurements

Diabetic children with poor glycemic control (group 3) had significantly lower mean 24-h R–R intervals than diabetic children with good glycemic control (group 2) over 24 h (620 ± 75 vs. 726 ± 52 ms, $p < 0.01$). SDRR was significantly lower in group 3 than group 2 and healthy age-matched controls (group 1) (117 ± 37 ms vs. 166 ± 33 ms and 174 ± 52 ms, $p < 0.05$). SDANN was also significantly lower in group 3 than group 2 (107 ± 37 ms vs. 150 ± 45 ms, $p < 0.05$). SD, rMSSD, and pNN50 values were significantly lower in diabetic children with poor glycemic control than the other two groups (Table 2).

Frequency-Domain Measurements

Low-frequency (LF) and high-frequency (HF) power of heart rate period are significantly lower in diabetic children with poor glycemic control than controls and other diabetic children (LF, 20 ± 8 ms vs. 34.7 ± 11.2 ms and 34 ± 8 ms; HF, 15 ± 8 ms vs. 34.4 ± 10.2 ms and 30 ± 9 ms, $p < 0.01$) (Figs. 1 and 4). The ratio of low- to high-frequency power was also lower in group 3 than group 1 (Table 2).

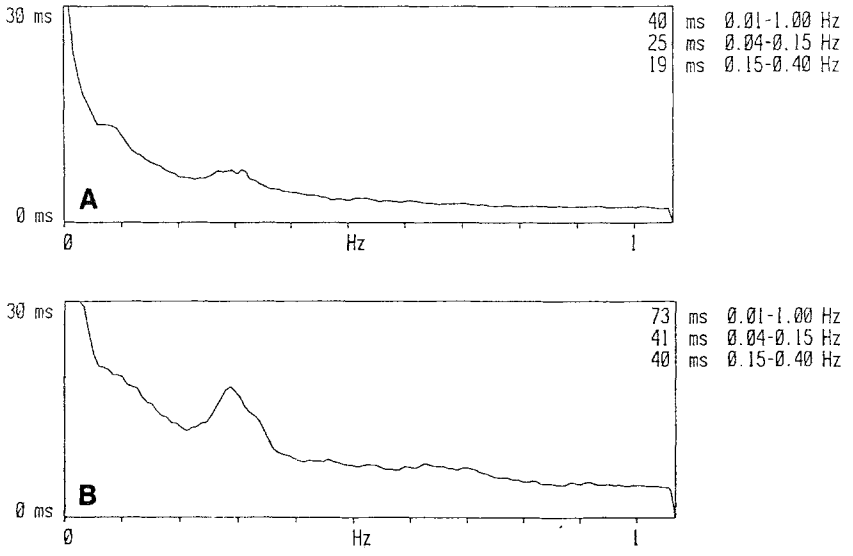

Fig. 1. Spectral analysis of heart rate power in children with poor glycemic control (**A**) and in diabetic children with good glycemic control (**B**) during the daytime and the nighttime (average). The high-frequency component (0.15–0.40 Hz) of the spectrum decreased significantly in diabetic children with poor glycemic control. The low-frequency component (0.04–0.15 Hz) of heart rate power spectrum and total heart rate power spectra (0.01–1.00 Hz) were also reduced in this children.

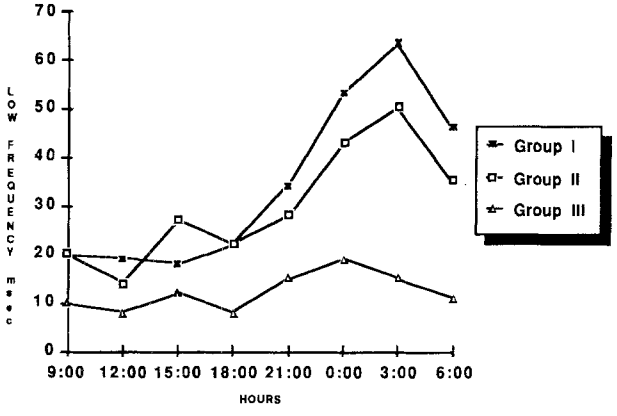

Fig. 2. Twenty-four-hour variation of low-frequency component in control group, diabetic children with and without good glycemic control. Each point is the mean hourly value. All points are significantly different in diabetic children with poor glycemic control. Abbreviations as in Fig. 1 and Table 1.

Normal children and diabetic children with good glycemic control had greater HRV as a measure of frequency-domain analysis. Both LF and HF component of heart rate power spectra showed a distinct 24-h variation (Figs. 2 and 3). However, these components demonstrated much less variation in diabetic children with poor glycemic control especially involving HF component.

Discussion

We used time- and frequency-domain methods to assess the HRV in children with diabetes and healthy age-matched children. Time-domain measurements in our study included six parameters. Mean R–R interval and standard deviation of the mean R–R interval (SDRR) are subject to all kinds of variation [4, 16, 24]. Most reports suggest these two parameters of HRV are closely related to cardiac autonomic function [16, 22, 29]. Standard deviation of R–R intervals during successive 5-min segments averaged over 24 h (SDANN) has been reported to be an index of vagal tone and is mostly likely to react heart rate changes due to changes in posture and activity [23, 27]. Martin et al. [23] reported that HRV as measured by SDANN was significantly lower in patients who died suddenly than in normal subjects. In our study group, there were lower SDANN values in diabetic children with poor glycemic than with good glycemic control (Table 2). However, the mean of all 5-min standard deviations of R–R intervals (SD) were also significantly lower in diabetic children with poor glycemic control. SD is sensitive to all higher frequency components except posture and activity changes [21, 23, 30, 31, 34].

In various studies there was a close relationship between low SD values and sudden cardiac death [21, 23, 30, 34]. Since SD is a powerful indicator of vagal activity, we suggest that poor metabolic control is diabetic children strongly related to vagal neuropathy. Cook et al. [3] showed that during atenolol treatment, which acts as a central parasympathomimetic agent, three measures of tonic vagal activity (pNN50, rMSSD, and high frequency component of heart rate power spectrum) were significantly increased. The pNN50 (proportion of adjacent R–R intervals more than 50 ms different) is a sensitive method to detect the cardiac parasympa-

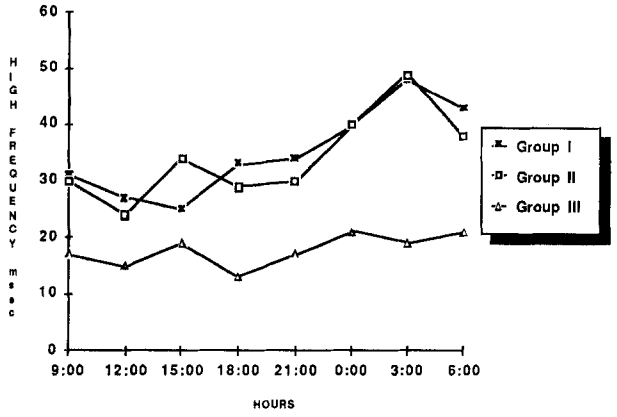

Fig. 3. Twenty-four-hour variation of high-frequency component in control group, diabetic children with and without good glycemic control. Each point is the mean hourly value. All points are significantly different in diabetic children with poor glycemic control. The difference is especially significant at nighttime, reflecting vagal neuropathy. Abbreviations as in Fig. 1 and Table 1.

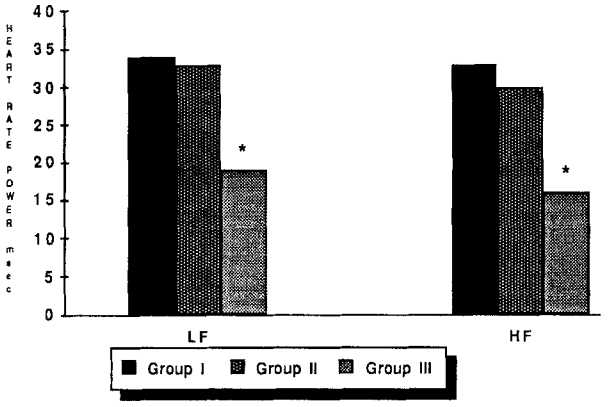

Fig. 4. Mean 24-h value of the low- (LF) and high- (HF) frequency components in control group and diabetic children with and without good glycemic control. $*p < 0.01$; other abbreviations as in Fig. 1 and Table 1.

thetic activity in diabetic patients [7, 9]. In our study, these three measures of parasympathetic tone were significantly lower in diabetic children with poor glycemic control than in other diabetic children and healthy children.

These parameters may thus be used to test for any subclinical cardiac autonomic neuropathy in diabetic children. We believe that time-domain values of HRV are more sensitive than conventional tests which have been used to detect the cardiovascular autonomic neuropathy. Since the vagus nerve is affected before the cardiac sympathetic nerves, these results show the value of these parameters in predicting cardiac autonomic neuropathy in diabetic children without clinical evidence of cardiovascular autonomic involvement [5, 6, 9, 29].

In an attempt to understand the neurohumoral mechanisms that modulate heart rate, spectral analysis has been used to define the frequency component of heart rate in animals [19, 26], healthy adults [1, 3, 28], neonates [10, 11, 32], children with heart disease [12], and with diabetes mellitus [19], as well as in adults after resuscitation from sudden death [2, 23]. HRV, defined by power spectral analysis, is severely reduced after cardiac transplantation and may predict rejection [30]. The low-frequency (LF) component has been proved to be a likely index of sympathetic activity, especially during standing. However, LF fluctuations in the supine position are mediated entirely by the parasympathetic nervous system [1, 28]. Cook et al. [3] showed a significant increase in LF power during the atenolol treatment. Besides this, high-frequency (HF) power is mediated solely by the parasympathetic nervous system [3]. Pomeranz et al. [28] showed that HF fluctuations at the respiratory band are decreased by standing. During sleeping hours, the respiratory peak is more prominent due to the supine position and an increase in parasympathetic tone.

There are much fewer studies concerning the spectral analysis of HRV in children [10–12, 19, 32]. Three reported papers investigated the association between the sudden infant death syndrome and the spectral analysis of HRV [10, 11]. They concluded that an abnormal pattern of HRV as a marker of sudden infant death syndrome in a referred high-risk infant population does not apparently predict this syndrome in the population at large [10, 11, 32]. Gordon et al. [12] showed that a persistently low LF/HF ratio <2.0 and decreased LF values are due to a diminution in autonomic regulation and strongly correlated with sudden cardiac death in critically ill children after cardiac surgery. There have been a few clinical studies to assess autonomic neuropathy in diabetic adults [18, 20]. In these reports, HRV, measured by the frequency domain method, decreased significantly as autonomic neuropathy became increasingly severe [18, 20]. The origins of this abnormal response have been traced to the parasympathetic portion of the autonomic nervous system. Kitney [18] used the frequency power spectrum to differentiate the HRV in diabetes from those in normals. There has been only one report about diabetic autonomic neuropathy in children which has examined the heart rate power spectrum: Lindqvist et al. [19] found HRV to be normal in diabetic children.

In our series, LF and HF components of heart

rate were significantly lower in diabetic children with poor glycemic control than in other diabetic children and in age-matched controls. The ratio of LF/HF was significantly lower in diabetic children with poor glycemic control than in healthy children (Table 2). These low- and high-frequency components of the heart rate power spectra showed much less 24-h variation in diabetic children with poor glycemic control (Figs. 2 and 3). This variation is extremely low in the HF component. Our results are similar to those of Kitney et al. [18] and Lishner et al. [20] in demonstrating a decrease in frequency-domain values of HRV in diabetic children with poor glycemic control.

In conclusion, time- and frequency-domain analysis of HRV can be used to asses the cardiac autonomic function in diabetic children. In this study, three features of time-domain analysis of HRV (SD, pNN50, rMSSD) and two features of frequency-domain analysis (LF, HF) were noted to correlate with subclinical autonomic neuropathy in children with diabetes mellitus. Significantly lower measurements may reflect the autonomic dysfunction in primarily vagal neuropathy. It remains to be determined whether changes in diabetic management can meaningfully change these measures of HRV.

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