Cardiac Autonomic Dysfunction in Diabetic Children

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OBJECTIVE — Adults with type 1 diabetes may have abnormal alterations in heart rate variability (HRV) due to cardiac autonomic neuropathy. This prospective study was performed to determine whether HRV can be used to detect subclinical autonomic neuropathy in diabetic children.

RESEARCH DESIGN AND METHODS — We examined five time domain and three frequency domain HRV indices determined from 24-h Holter recordings in 73 diabetic children and adolescents aged 3–18 years (mean 12.1 years) with a mean duration of diabetes of 55 months. The measures were compared with normal ranges. *Z* scores were established for each parameter and were compared with classic risk factors of other diabetic complications.

RESULTS — Most HRV indices were significantly depressed in children aged ≥11 years, and the levels of HRV abnormalities were significantly correlated with long-term metabolic control (mean GHb for 4 years) in that age-group. In younger patients, HRV indices were within the normal range and were not correlated with the level of metabolic control. Illness duration and microalbuminuria but not short-term metabolic control (most recent GHb) were also independently predictive of HRV abnormalities.

CONCLUSIONS — These results suggest that early puberty is a critical period for the development of diabetic cardiac autonomic dysfunction. Therefore, all type 1 diabetic patients should be screened for this complication by HRV analysis beginning at the first stage of puberty regardless of illness duration, microalbuminuria, and level of metabolic control.

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Studies in adult patients have shown that autonomic neuropathy is a frequent complication of diabetes that contributes significantly to morbidity and mortality. Autonomic neuropathy can cause disturbances in the function of the cardiovascular, gastrointestinal, and genitourinary systems; in pupillary and sweating function; and in the counterregulatory hormonal response to hypoglycemia.

Heart rate variability (HRV) is increasingly recognized as a measure of cardiac autonomic control, and HRV abnormalities have been documented in adult patients with diabetic autonomic neuropathy (1,2). However, few reports are available regarding the use of HRV in diabetic children (3–5). Therefore, we investigated cardiovascular autonomic function in a large cohort of children and adolescents with stable type 1 diabetes to assess the prevalence of subclinical autonomic neuropathy and to evaluate factors associated with autonomic abnormalities.

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Abbreviations: ECG, electrocardiogram; HRV, heart rate variability.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Patients

A total of 75 children and adolescents with stable type 1 diabetes were prospectively recruited from the diabetes population that regularly attends our outpatient clinic. Holter monitoring was recorded for 24 h after sinus rhythm was confirmed by a 12-lead electrocardiogram (ECG). Two patients were excluded because their Holter recordings revealed frequent extrasystoles. A quality analysis of 24-h HRV was then performed in the 73 remaining patients who were aged 3–18 years (mean ± SD 12.1 ± 4.6). Diabetes duration ranged from 2 to 183 months (54.9 ± 42.7). The vast majority of patients had been treated with combinations of short- and intermediate-acting human insulin injected subcutaneously two times a day. Metabolic control was satisfactory in all patients. No patients had markedly increased microalbuminuria (the maximal observed value was 65.2 mg/24 h), and the mean GHb value during the 4-year period preceding the Holter recordings was 7.9 ± 1.2% in absolute value or 101.1 ± 36.7% in deviation to the mean reference value. None of the subjects had any disorders other than diabetes or took medications. The diabetic children did not have any clinical complications or overt diabetic nephropathy, retinopathy, or neuropathy. All participating patients had no family history of hypertension or cardiovascular or renal disease.

Holter monitoring

Continuous ambulatory ECG monitoring was recorded during a 24-h period by using an MR45 Oxford recorder (Oxford Instruments, Largo, FL). The tape recording consisted of two channels of ECG data. The data were recorded while the children performed their usual daily activities. The parents were informed about the purpose of the study and gave their consent for their children's participation.

Analysis of recordings

All Holter tapes were analyzed by using a Medilog Excel 2.0 computer program (Oxford Instruments) to identify each QRS

Table 1—*Definition of the time and frequency domain measures*

Parameter	Definition
SDNN	SD of all RR intervals for 24 h
SDNNi	Mean of the SD of all RR intervals for all 5-min segments of the analysis
SDANNi	SD of the means of all RR intervals for all 5-min segments of the analysis
rMSSD	Square root of the mean of the sum of squares of differences between adjacent RR intervals during the length of the analysis
pNN50	Percentage of differences between adjacent RR intervals that are >50 ms for the entire analysis
LF	Low-frequency index (0.04–0.15 Hz)
HF	High-frequency index (0.15–0.4 Hz)
LF/HF ratio	Low- to high-frequency index ratio

Table 2—*Z scores of HRV indices in our diabetic population*

Parameter	*Z* score for age	*Z* score for mean RR interval
SDNN	−0.23 ± 0.95*	−0.58 ± 1.11*
SDNNi	−0.20 ± 0.86*	−1.12 ± 1.14*
SDANNi	−0.18 ± 1.00	−0.34 ± 1.07*
rMSSD	−0.25 ± 0.92*	−0.87 ± 1.14*
pNN50	−0.27 ± 0.99*	−0.97 ± 1.13*
LF	0.08 ± 1.05	0.18 ± 0.92
HF	−0.19 ± 1.14	−0.28 ± 1.31*
LF/HF	1.00 ± 2.00*	0.85 ± 1.77*

Data are means ± SD. Calculation of *Z* scores as explained in the text according to the patient age and the 24-h mean RR interval. Normal values for each parameter are 0.00 ± 1.00. *$P < 0.05$.

Table 3—R *values for the correlations between HRV indices and risk factors*

Patients	Age of patients	Diabetes duration	Microalbuminuria	4 Years of GHb
n	73	73	49	27 (aged 11–18 years)
SDNN-A	0.24*	0.21	0.51†	0.28
SDNNi-A	0.26*	0.25*	0.52†	0.45†
SDANNi-A	0.23*	0.18	0.54†	0.21
rMSSD-A	0.46†	0.19	0.57†	0.37*
pNN50-A	0.49†	0.28*	0.53†	0.36*
LF-A	0.23*	0.21	0.48†	0.52†
HF-A	0.49†	0.09	0.53†	0.48†
LF/HF-A	0.60†	0.29*	0.38†	0.19
SDNN-RR	0.29*	0.11	0.58†	0.20
SDNNi-RR	0.45†	0.26*	0.60†	0.45†
SDANNi-RR	0.23*	0.10	0.46†	0.17
rMSSD-RR	0.57†	0.18	0.56†	0.38*
pNN50-RR	0.53†	0.24*	0.59†	0.38*
LF-RR	0.28*	0.17	0.49†	0.46†
HF-RR	0.56†	0.29*	0.51†	0.35*
LF/HF-RR	0.51†	0.23*	0.35†	0.13

Data are correlation coefficients. *$P < 0.05$; †$P < 0.01$.

complex. All data were reviewed by one analyst and then edited. More than 23 h of analyzable data were necessary for the 24-h recording to be accepted for the study. Artifacts and ectopic complexes were rejected. HRV measures were calculated by using only normal-to-normal intervals. For the frequency domain analysis, beat-to-beat fluctuations were transformed by fast Fourier transformation, and the specific measures were computed as the square root of the areas under the power spectrum. The recommendations of the Task Force of the European Society of Cardiology were respected (6).

HRV indices

Five time domain measures (SDNN, SDNNi, SDANNi, rMSSD, pNN50) and three frequency domain measures (LF, HF, LF/HF ratio) were examined (Table 1). All indices were automatically calculated with the Medilog Excel computer program and compared with parameters of HRV that we previously established in 210 healthy nondiabetic children and teenagers (7).

Glycemic control was assessed by GHb level at every routine clinic visit (every 2–3 months) and was measured with the turbidimetric inhibition immunoassay (Boehringer Mannheim, Mannheim, Germany). Glycemic control was expressed as the percentage of deviation to the mean control levels. The 24-h urine collections were performed in 49 patients who also agreed to participate in this part of the study. Microalbuminuria was measured by immunonephelometry with N albumin kits (Behring, Somerville, NJ) and expressed in milligrams per day (normal range <16 mg/day).

Statistical analysis

Normal ranges of HRV were established for each parameter according to the mean RR interval for the length of the analysis and according to the age of the patients because a multiple correlation analysis showed the independent effect of both factors on HRV in a healthy pediatric population (7). A *Z* score was then calculated for each parameter of our diabetic patients according to both factors. The *Z* score is the difference between an individual value and the mean normal value normalized by the SD of the mean in the normal population [$Z = (X - M)/\text{SD}$, where X is the observation and M is the mean normal value]. The *Z* score for an item indicates how far and in what direction that item deviated from the distribution's mean and is expressed in units of SD. Statistical associations between normalized HRV indices and type 1 diabetes duration, age of the patients, 24-h microalbuminuria, and parameters of the metabolic control (most recent GHb and average GHb during the 4-year period preceding the dataset collection) were estab-

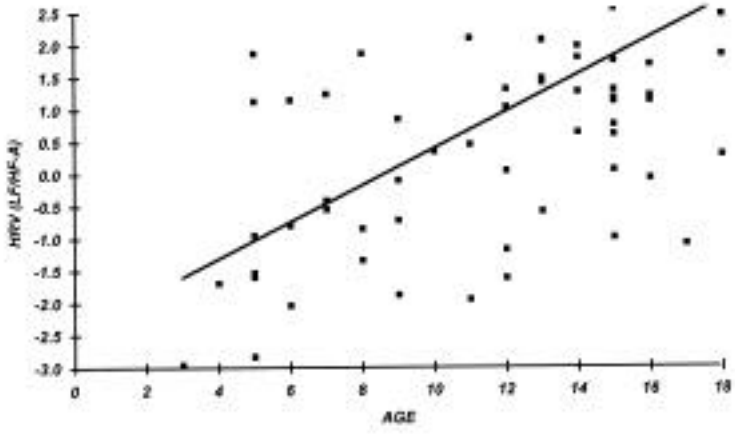

Figure 1—*Correlation between LF/HF ratio (Z score according to age) and patient age (in years).*

lished by linear regression analysis for continuous data. Then *r* values were calculated, and differences at the 5% level were considered significant. Multiple regression analysis was used to test the independence of the influence of those factors on HRV indices.

RESULTS — Despite good metabolic control, HRV was significantly reduced in our diabetic population (Table 2). Most of the HRV indices were significantly smaller than in control subjects, and the balance LF/HF was very significantly elevated. This balance and the time domain parameters normalized for the mean RR interval during the length of the analysis seem to be more sensitive in detecting cardiac dysautonomia in young diabetic patients.

Our data showed a significant negative correlation (except for the balance LF/HF, for which a positive correlation is shown) between all normalized HRV indices and the age of the patients (Table 3). The correlation was significant at the 1% level for the parameters influenced by the vagal activity (rMSSD, pNN50, HF, and LF/HF) (Fig. 1) and was significant at the 5% level for the other indices. Interestingly, all indices were within the normal range for children aged ≤10 years, whereas 27 of the 50 patients aged ≥11 years had at least one abnormal test result (*Z* score of more than 2 SD for the LF/HF ratio, *Z* score of less than −2 SD for the other indices) (Fig. 2). No sex differences were observed except in patients aged 11–13 years; in that age-group, 5 of 9 girls but only 1 of 6 boys had at least one abnormal test result.

Our data also showed a significant negative linear correlation at the 5% level between SDNNi, pNN50, and HF and duration of type 1 diabetes (Table 3 and Fig. 3) and a positive linear correlation between LF/HF ratio and illness duration (Table 3).

No correlation was found between HRV indices and short-term (most recent GHb) or long-term (averaged GHb for 4 years) metabolic control. However, we found a significant correlation between the level of HRV abnormalities and the long-term metabolic control in the group of patients aged ≥11 years (Fig. 4 and Table 3).

Finally, our data showed a strong negative linear correlation at the 1% level between all HRV indices (except for the balance LF/HF, for which the correlation is positive) and 24-h microalbuminuria (Fig. 5 and Table 3).

We also found some correlations at the 5% level between the following risk factors: age and illness duration ($r = 0.29$, $n = 73$), age and microalbuminuria ($r = 0.31$, $n = 49$), illness duration and microalbuminuria ($r = 0.24$, $n = 49$), and, for patients aged ≥11 years, mean GHb for 4 years and microalbuminuria ($r = 0.43$, $n = 19$). However, a multiple regression analysis confirmed the independence of the influence of these risk factors on the HRV.

CONCLUSIONS — Diabetic autonomic neuropathy is a recognized complication of type 1 diabetes. Simple bedside tests (8–11) are widely available to diagnose autonomic neuropathy, but selecting appropriate tests for use in routine pediatric practice remains difficult because the Ewing battery of tests (12) is cumbersome, time consuming, and not very sensitive because of reflex compensatory mechanisms and a lack of cooperation from children. Pupillometry (13–16) and studying urinary bladder function (17) have demonstrated autonomic dysfunction in type 1 diabetic children but do not demonstrate cardiac autonomic control.

Clinicians should be able to determine cardiac autonomic neuropathy by using a method that is easy to perform, sensitive,

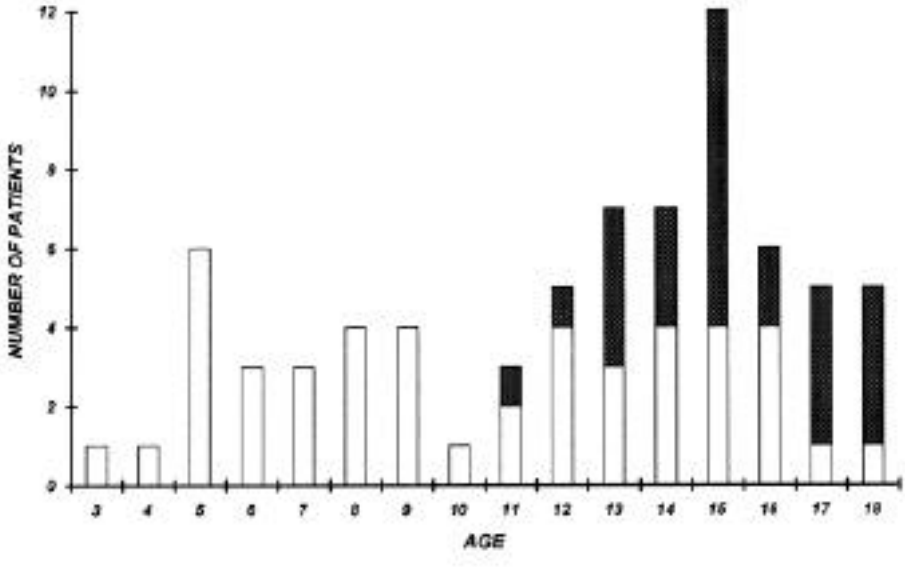

Figure 2—*Relationship between pathological HRV and age.* □*, Number of patients with all HRV indices within the normal range;* ■*, number of patients with at least one pathological value according to age.*

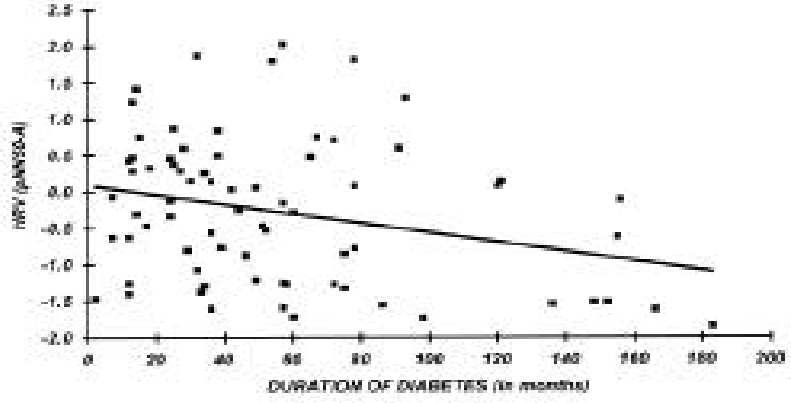

Figure 3—*Correlation between pNN50 (Z score according to age) and duration of diabetes (in months).*

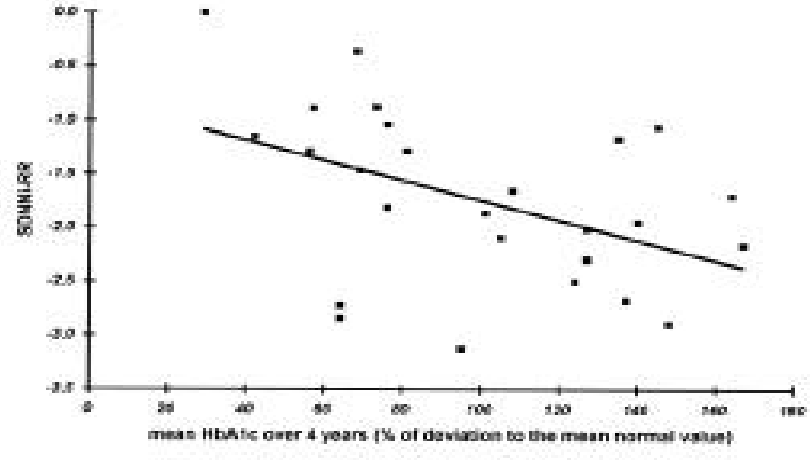

Figure 4—*Correlation between SDNNi (Z score according to the mean RR interval) and the mean GHb value for 4 years (percentage of deviation to the mean normal value) in patients aged ≥11 years.*

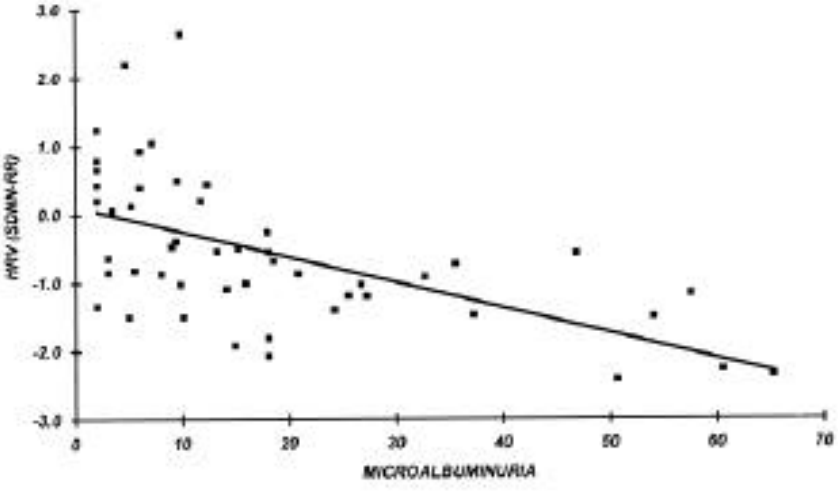

Figure 5—*Correlation between SDNN (Z score according to the mean RR interval) and 24-h micro - albuminuria (in milligrams per 24 h).*

reproducible, noninvasive, and independent of the patient's cooperation. HRV, as determined from 24-h Holter recordings, depends on the influence of sympathetic and vagal activity on the sinus node. HRV analysis can characterize and quantify variations in sympathetic and vagal activity and has been used to foster a better understanding of physiological and pathological processes in adults (18) and in children (19,20). HRV analysis has been performed in diabetic adults in whom abnormalities were shown to be consistent over time (21) and in diabetic children (3) to evaluate autonomic dysfunction in young patients with poor metabolic control.

Our results can be interpreted as evidence of early cardiac autonomic neuropathy in young patients with type 1 diabetes, even in patients with good metabolic control. Time domain parameters normalized for the mean RR interval, especially those representing the vagal activity and the balance LF/HF, are the first indices of cardiac dysautonomia in young diabetic patients.

Data on the influence of risk factors on autonomic abnormalities are conflicting, as are data for other complications of type 1 diabetes. Previous studies have suggested an association with poor metabolic control (3,4,8,11,14,15,17), age (22), and longer diabetes duration (4,8,11,14, 15,17,23). No association was found in other studies (9,24–26). Progression has been observed in patients with poor glycemic control (27).

Our findings support the view that the development of autonomic complications depends on type 1 diabetes duration and patient age. The advancement of pubertal stages has been previously associated with peripheral and autonomic neuropathy in most (28–30) but not all (8,13) studies. The depressed HRV and its correlation with the level of long-term metabolic control in children aged ≥11 years, but not in younger children, suggest that puberty is a critical period for the development of autonomic neuropathy; however, this does not mean that the contribution is minimal during the prepubertal years of type 1 diabetes. HRV abnormalities were correlated with the mean GHb during a 4-year period, so intensive diabetes treatment in the prepubertal years is certainly important. Our experience with this method in very young children with heart disease (19,20) contradicts the hypothesis that the method may be less sensitive in younger

patients. In the present study, puberty did not coincide with a certain critical duration of illness, and sex differences were only observed in patients aged 11–13 years, which reinforces the hypothesis of the primary role of puberty.

Microalbuminuria proved to be independently predictive of autonomic dysfunction, so this correlation cannot be related to the influence of long-term metabolic control from early puberty on both complications. The same pathological processes, such as microvascular complications related to pubertal changes (28,29), may lead to neuropathy and nephropathy. Autonomic dysfunction, by reducing the nocturnal fall in blood pressure, may also facilitate the development of nephropathy by increasing the intraglomerular pressure (31).

Enzymatic activation resulting from chronic hyperglycemia and microvascular abnormalities plays an important role in the progressive damage of nerve fibers in patients with longstanding type 1 diabetes, and other factors certainly also contribute (32). Early abnormalities are of functional origin, result from endoneural edema or intra-axonal sodium accumulation (33), and are reversible through intensified glycemic control (34). Their progression to the irreversible structural phase may be facilitated by hormonal changes during puberty and also by prolonged periods of poor metabolic control, which are rare before puberty. Early detection of cardiac autonomic dysfunction may be important to further motivate patients to improve their diabetes control and hopefully to delay the development of complications. However, whether changes in management can meaningfully change or even reverse the spontaneous evolution of dysautonomia and whether early HRV abnormalities are accurate predictors of later symptomatic autonomic neuropathy remain to be determined.

The results of this study can be interpreted as evidence of early cardiac autonomic neuropathy in young diabetic patients. Therefore, all type 1 diabetic patients should be screened by HRV analysis for that complication beginning at the first stage of puberty regardless of illness duration, microalbuminuria, and level of metabolic control.

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