ORIGINAL ARTICLE

Impact of Glycemic Control, Disease Duration, and Exercise on Heart Rate Variability in Children with Type 1 Diabetes Mellitus

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Background/Purpose: Type 1 diabetes is commonly associated with autonomic neuropathy. The present study investigated the influences of glycemic control, disease duration (DD), and exercise on autonomic nervous function in children with type 1 diabetes by analysis of their heart rate variability (HRV).

Methods: Seventy-nine type 1 diabetic children were recruited and categorized into four groups by HbA1c of 8% and DD of 4.5 years. HRV parameters as determined by separate frequency domain components (low frequency: LnLF, 0.04–0.15 Hz; high frequency: LnHF, 0.15–0.5 Hz; total power: LnTP, 0.04–0.5 Hz) were measured both at rest and during exercise. Pearson's correlation, one-way ANOVA, and multiple regressions with stepwise method were used for statistical analysis.

Results: While at rest, HbA1c and DD were negatively correlated with all HRV parameters. Both HbA1c and DD were significant predictors in LnTP. However, only HbA1c was a significant predictor in LnLF and LnHF. Type 1 diabetes patients with HbA1c > 8% and DD > 4.5 years had a significantly lower HRV than the other patients. During exercise, HRV reduced significantly and no significant correlation between HbA1c and HRV or between DD and HRV was observed. Also, a significant difference in HRV among the four groups was not demonstrated. The smallest decrement in HRV from resting to exercise were in subjects with HbA1c > 8% and DD > 4.5 years.

Conclusion: HbA1c was a more dominant predictor for LnTP, LnHF and LnLF than DD in children with type 1 diabetes at rest. HRV reduced significantly from resting to exercise. However, the responses of HRV during exercise differ from the responses of HRV at rest. [*J Formos Med Assoc* 2007;106(11):935–942]

Key Words: disease duration, exercise, HbA1c, heart rate variability, type 1 diabetes

Diabetes is a metabolic disorder in which the body fails to produce enough insulin. Type 1 diabetes is the result of an autoimmune process, which leaves the patient dependent on insulin injections for survival.[1] The incidence of type 1 diabetes is much lower than that of type 2 diabetes, but the earlier onset and higher degree of glycemic exposure in type 1 diabetes place patients at a substantial risk for serious morbidities and earlier than expected mortality.[2]

Autonomic neuropathy is a common complication of diabetes. Extensive involvement of the autonomic nervous system in diabetic patients produces a variety of physiologic changes, which may include the electrical and contractile activity of the myocardium.[3] In patients with type 1 diabetes,

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subclinical signs of cardiovascular autonomic neuropathy (CAN) were detectable in 20–36% of individuals.[4] Once the diagnosis of CAN is established, a high mortality rate ranging from 27% to 56% will ensue.[5,6]

Heart rate variability (HRV) has been widely applied to assess autonomic nervous function by analyzing the frequency components of oscillation in RR intervals of electrocardiography (ECG).[7] With regard to HRV parameters, high frequency (HF; 0.15–0.5 Hz) mainly reflects parasympathetic nervous activities; low frequency (LF; 0.04–0.15 Hz) reflects chiefly sympathetic and a friction of parasympathetic nervous activities; while total power (TP; 0.04–0.5 Hz) represents overall autonomic nervous activities.[8] Abnormal HRV can be detected in diabetic subjects even when the clinical signs of CAN are obscure.[9–13] HRV analysis has been demonstrated to be more sensitive than traditional cardiovascular reflex tests in the clinical evaluation of autonomic nervous function.[9,10,14,15]

The pathogenesis of CAN in diabetes remains poorly understood. Neural damage by chronic hyperglycemia, vascular insufficiency, and autoimmune mechanisms have been suggested as plausible causes.[16–18] A previous study has demonstrated that extended disease duration (DD) and poor glycemic control are related to diminished HRV in type 1 diabetes.[11,13] However, the concurrent effects of glycemic control and DD on HRV have not been addressed. In addition, exercise is usually advocated for diabetic patients, but little is known about the change in HRV during exercise in type 1 diabetes. The purpose of this study was to determine the impacts of glycemic control and DD on HRV parameters at the same time. In addition, the response of HRV during exercise in children with type 1 diabetes was also examined.

Materials and Methods

Subjects and grouping

Seventy-nine subjects aged 8–13 years with type 1 diabetes were recruited from a pediatric diabetic clinic in a tertiary medical center in Taiwan. Type 1 diabetes was diagnosed on the basis of clinical and laboratory evidence. Patients presented with polyuria, polydipsia, and weight loss with/without polyphagia. They had hyperglycemia (glucose > 200 mg/dL) and ketosis with/without acidosis. Those who had acanthosis nigricans, hematologic disorders, Prader-Willi syndrome or Turner syndrome and those who were taking steroid or growth hormone therapy were excluded. Anti-islet autoantibodies including glutamic acid decarboxylase and insulinoma-associated antigen-2 were also measured in all enrolled children. In the study, all subjects were receiving regular insulin treatments. This study was approved by the human investigation committee of the hospital, and written informed consent was obtained from all subjects and their parents before their participation.

HbA1c tested within 1 month and DD were obtained from the medical charts. In terms of the recommendation of the American Diabetes Association, HbA1c of school-aged diabetic children should be ≤ 8%.[19] Therefore, the adequacy of glycemic control was determined by the cut-off value of 8%. All subjects had a DD ranging from 1.0 to 12.0 years, and we adopted 4.5 years, the median of our study group, as the dividing point for grouping. Subjects were then categorized into group I ($n = 16$, HbA1c ≤ 8%, DD ≤ 4.5 years), group II ($n = 15$, HbA1c ≤ 8%, DD > 4.5 years), group III ($n = 21$, HbA1c > 8%, DD ≤ 4.5 years), and group IV ($n = 27$, HbA1c > 8%, DD > 4.5 years).

HRV analysis

Standard three-channel ECG electrodes were attached to the anterior chest wall of subjects and connected to the monitor system (Acqknowledge III, MP150WSW; BIOPAC System, Santa Barbara, CA, USA). All QRS complexes from ECG were first edited automatically and then manually by careful inspection of the RR intervals. Signals were digitalized at 500 Hz and transformed into a spectrum by Fast Fourier Transformation. Separate frequency components of the HRV were obtained

including LF, HF and TP. These HRV parameters were then logarithmically transformed (Ln) to control for the skewed distributions.

Experimental protocol

All procedures were performed in a quiet room, with the temperature maintained at 21–26°C. At the study entrance, the age, gender, body height, body weight, body mass index (BMI), waist/hip ratio (WHR), HbA1c, and DD were documented. Beverages rich in caffeine content and vigorous exercise were prohibited in the 2 hours before testing. The ECG was recorded at rest and during exercise. All subjects were asked to stand still for 10 minutes at rest, followed by exercise with a fixed rhythm on a stair-stepper (JK-355c; JKexer Inc., Taipei, Taiwan) for 10 minutes. ECG was continuously monitored throughout the test. HRV analysis was based on the last 5 minutes of recordings of the steady ECG in each section.

Statistical analysis

SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for data analysis. Data were expressed as mean ± standard deviation (SD). Pearson's correlation was used to examine the relationships between HRV and HbA1c or DD. Differences in HRV among the four groups were determined by one-way ANOVA. *Post hoc* analysis for multiple comparisons of means was performed using Scheffé's test. Multiple regressions with stepwise method were conducted to determine the predictors of HRV. A p value < 0.05 was considered statistically significant.

Results

Seventy-nine children (37 males, 42 females) with type 1 diabetes participated in this study. The overall mean age was 10.3 ± 1.3 years. The average body height and weight were 137.0 ± 9.4 cm and 34.7 ± 8.6 kg, respectively. Mean BMI was 18.3 ± 3.2 kg/m^2, and mean WHR was 0.8 ± 0.1. HbA1c ranged between 6.3% and 17.2%, with a mean of 9.3 ± 2.4%. DD ranged between 1.0 and 12.0 years, with a mean of 4.2 ± 2.6 years. Of the 79 children, 65 (82.3%) were positive for at least one of the measured autoantibodies. No significant difference in gender, age, body height, body weight, BMI, and WHR was observed among the four groups (Table 1).

The mean HbA1c and DD were 7.2 ± 0.5% and 2.1 ± 1.2 years for group I, 7.5 ± 0.5% and 6.5 ± 1.4 years for group II, 10.4 ± 2.3% and 2.4 ± 1.2 years for group III, and 10.9 ± 2.2% and 6.8 ± 1.8 years for group IV, respectively.

Impact of HbA1c and DD on HRV

There were significant negative correlations between HbA1c and all HRV parameters at rest in children with type 1 diabetes (Figure 1). The estimated regression equations were y = 7.64 − 0.16x (r = −0.46, $p < 0.001$) in LnLF, y = 6.71 − 0.18x

Table 1. Characteristics of subjects*

Variables	Group I (n = 16)	Group II (n = 15)	Group III (n = 21)	Group IV (n = 27)	p
Gender (M/F)	6/12	8/5	11/15	12/10	0.36
Age (yr)	9.6 ± 1.0	9.7 ± 1.5	10.1 ± 1.2	10.6 ± 1.4	0.08
Height (cm)	137.3 ± 9.0	135.5 ± 9.2	138.2 ± 9.4	136.2 ± 10.1	0.82
Weight (kg)	35.9 ± 9.6	33.5 ± 8.9	35.7 ± 8.6	33.1 ± 7.7	0.64
BMI (kg/m^2)	18.9 ± 3.7	18.0 ± 2.4	18.5 ± 3.5	17.7 ± 2.9	0.63
WHR	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.49
HbA1c (%)	7.2 ± 0.5	7.5 ± 0.5	10.4 ± 2.3	10.9 ± 2.2	
Disease duration (yr)	2.1 ± 1.2	6.5 ± 1.4	2.4 ± 1.2	6.8 ± 1.8	

**Data are presented as mean ± standard deviation or n. BMI = body mass index; WHR = waist/hip ratio.*

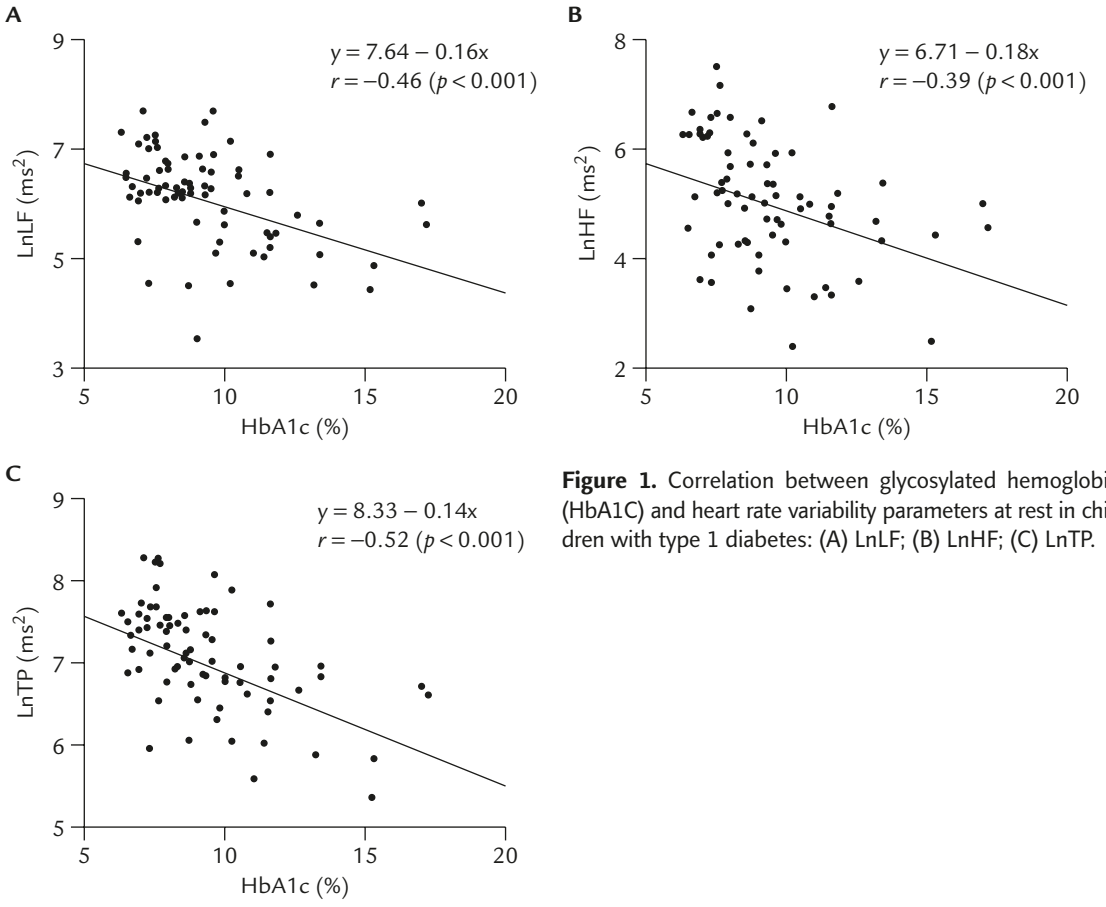

Figure 1. Correlation between glycosylated hemoglobin (HbA1C) and heart rate variability parameters at rest in children with type 1 diabetes: (A) LnLF; (B) LnHF; (C) LnTP.

($r=-0.39$, $p<0.001$) in LnHF, and $y=8.33-0.14x$ ($r=-0.53$, $p<0.001$) in LnTP. However, no significant correlations were observed during exercise for LnLF ($r=-0.14$, $p=0.20$), LnHF ($r=-0.16$, $p=0.16$), or LnTP ($r=-0.09$, $p=0.41$).

There were negative correlations between LnHF and DD as well as LnTP and DD, but not between LnLF and DD in children with type 1 diabetes at rest (Figure 2). The estimated regression equations were $y=5.51-0.09x$ ($r=-0.23$, $p=0.039$) in LnHF and $y=7.34-0.14x$ ($r=-0.27$, $p=0.018$) for LnTP. During exercise, no significant correlation between DD and any HRV parameters could be demonstrated.

To determine the concurrent effects of glycemic control and DD on HRV parameters, a series of multiple regressions with stepwise method were performed. Only HbA1C was a significant predictor in LnHF ($F=13.831$, $p<0.0001$) and LnLF ($F=20.808$, $p<0.0001$) (Table 2). Both HbA1C and DD were significant predictors in LnTP ($F=18.370$, $p<0.0001$). No significant relationship between HbA1c and DD ($r=0.1$, $p=0.38$) was observed in this study.

Comparison of HRV at rest and during exercise among groups

The HRV of the four study groups both at rest and during exercise are shown in Figure 3. While at rest, LnLF was significantly lower in group IV than in groups I, II and III (5.5 ± 0.9 *vs.* 6.6 ± 0.5, 6.4 ± 0.7 and 6.3 ± 0.6, respectively). Similar results were obtained for LnHF (4.3 ± 0.9 *vs.* 5.9 ± 0.9, 5.4 ± 1.0 and 5.9 ± 0.9, respectively) and LnTP (6.6 ± 0.6 *vs.* 7.6 ± 0.4, 7.2 ± 0.5 and 7.2 ± 0.4, respectively).

All HRV parameters during exercise were lower than they were at rest. No significant differences in HRV parameters were demonstrated during exercise among the four study groups. However, the percentage of decrease from resting to exercise in LnLF, LnHF and LnTP was smaller in group IV

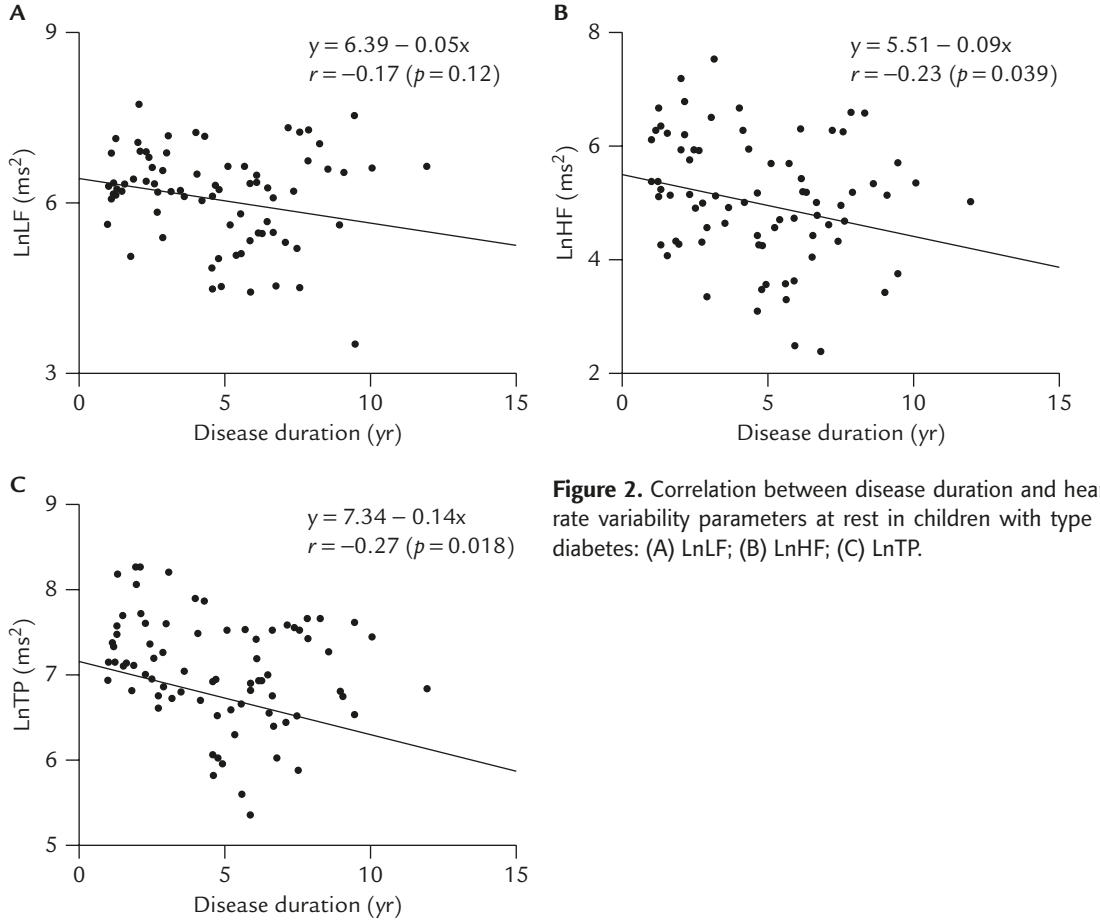

Figure 2. Correlation between disease duration and heart rate variability parameters at rest in children with type 1 diabetes: (A) LnLF; (B) LnHF; (C) LnTP.

Table 2. Stepwise regression analysis of heart rate variability

Dependent variable	Independent variable	B	Beta	Adjusted accumulated R^2	*t*
LnTP	HbA1C	−0.132	−0.508	0.270	−5.365*
	Disease duration	−0.050	−0.216	0.308	−2.280†
LnHF	HbA1C	−0.175	−0.390	0.141	−3.719*
LnLF	HbA1C	−0.161	−0.461	0.203	−4.562*

*$p < 0.0001$; †$p < 0.05$.

(27%, 51% and 26%, respectively) than in group I (35%, 51% and 30%, respectively), group II (38%, 59% and 32%, respectively), and group III (38%, 64% and 32%, respectively).

Discussion

Our data showed that HRV parameters, including LnLF, LnHF and LnTP, were all negatively correlated with HbA1c in type 1 diabetic children at rest, suggesting that autonomic nervous function was adversely affected by poor glycemic control. These findings are in agreement with previous research by Rollins et al who reported a negative correlation between HbA1c and HRV in type 1 diabetes.[20] It was also found that patients with type 1 diabetes were less likely to develop abnormal RR interval variations if they received intensive glycemic control.[21] Although Wawryk et al reported a contradictory result that reduced HRV was not associated with short-term or long-term metabolic control, they conceded that their subjects were relatively well controlled, which possibly

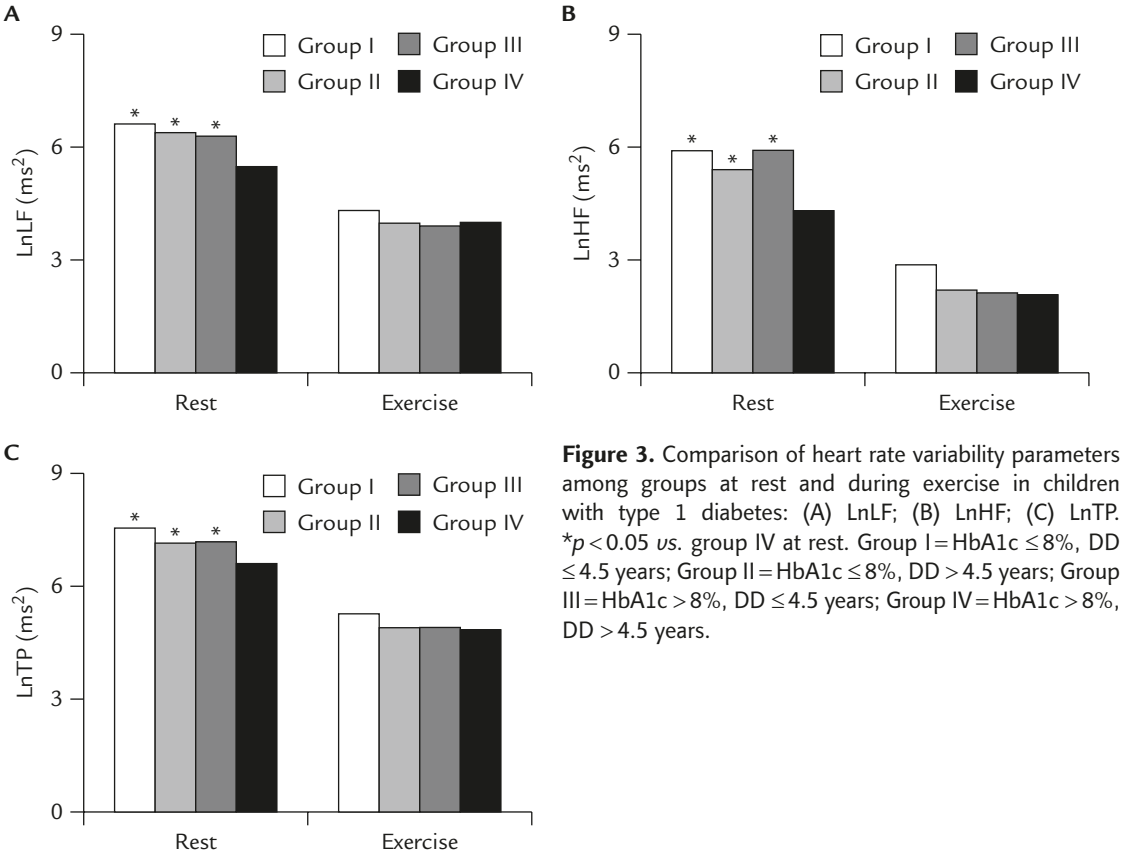

Figure 3. Comparison of heart rate variability parameters among groups at rest and during exercise in children with type 1 diabetes: (A) LnLF; (B) LnHF; (C) LnTP. *$p < 0.05$ *vs.* group IV at rest. Group I = HbA1c ≤ 8%, DD ≤ 4.5 years; Group II = HbA1c ≤ 8%, DD > 4.5 years; Group III = HbA1c > 8%, DD ≤ 4.5 years; Group IV = HbA1c > 8%, DD > 4.5 years.

dimmed their correlation.[11] CAN in diabetes is thought to occur at least in part due to the effect of hyperglycemia through the accumulation of reduced sugars in diabetic nerves. The neuropathogenic effect may then be triggered by hyperosmolarity, a change in the reductive–oxidative state, reduced nitric oxide synthesis, or vascular dysfunction.[22]

Our results indicated that autonomic neuropathy was more likely to occur with extended DD in type 1 diabetes. This finding was consistent with an early report by Valensi et al, which showed that the prevalence of CAN was correlated with diabetic duration.[23] Rollins et al also reported a similar result of the mean HRV in patients with DD > 3 years being significantly lower in comparison with control subjects.[20] A significant correlation between DD and LnHF rather than LnLF was observed in our study, which implied that the early impairment of the autonomic nervous system in diabetes lay mainly in the parasympathetic component.[10,24] The long-term effect of diabetes on HRV has been reported by Burger et al who investigated HRV in 23 diabetic patients with a DD > 24 years.[25] In their series, all of the HRV parameters were markedly decreased in comparison with the normal controls, which might imply further deterioration of parasympathetic activity or the overall involvement of the autonomic nervous system.

The major purpose of our study was to examine the concurrent influence of HbA1C and DD on HRV in type 1 diabetes. Based on the results of a series of multiple regression analyses, it was demonstrated that HbA1c was a more dominant predictor in LnTP, LnHF and LnLF than DD. In addition, subjects were classified into four groups according to their glycemic control and DD. The results indicated that children with HbA1c > 8% and DD > 4.5 years were more likely to be affected by CAN. The HRV of the remaining three groups, however, did not significantly differ at rest. These findings suggest that no matter how long the DD, early and intensive care in glycemic control is

a key factor for preventing the occurrence of CAN in type 1 diabetes.

Although a normal cardiovascular response to parasympathetic withdrawal resulting in increased heart rate and greatly reduced HRV during exercise in healthy populations have been reported in previous studies,[26,27] the changes in HRV during exercise in diabetic patients have not yet been elucidated. In our study, a similar result in terms of a decrease in HRV during exercise was observed and the smallest decrement in HRV from resting to exercise was demonstrated in group IV (HbA1c > 8%, DD > 4.5 years). However, no significant correlation between HbA1c and HRV or between DD and HRV was further observed during exercise. Also, a significant difference in HRV among the four groups was not demonstrated. A short exercise for only 10 minutes and absolute exercise intensity rather than relative exercise intensity performed by each subject may have contributed to these results. A recent study conducted by Dewey et al revealed that greater exercise-induced HRV during peak exercise was related to increased risks for all-cause and cardiovascular mortality.[28] These results contrast to those found during rest. Therefore, it was suggested that exercise draws out a different pattern of autonomic and non-autonomic modulation. And it is not easily accounted for by current explanations for resting HRV. The response of HRV to exercise reflects their autonomic nervous function and may be useful for finding patients who are at risk of subsequent mortality.

We conclude that at rest, HbA1c was a more dominant predictor in LnTP, LnHF and LnLF than DD in children with type 1 diabetes. HRV reduced significantly from resting to exercise. However, the responses of HRV during exercise differ from the responses of HRV at rest.

The main limitation of the study was the use of a single HbA1c test as an indicator of glycemic control over DD. HbA1c reflects the average blood sugar control for the past 2–3 months, and the average of a series of regular HbA1c tests would have been more representative of overall glycemic control. Nevertheless, the interval of HbA1c tests usually depends on the clinical results of diabetic control and a selection bias may still occur.

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