Impaired Diurnal Cardiac Autonomic Function in Subjects With Type 2 Diabetes

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OBJECTIVE — To assess diurnal cardiac sympathetic and parasympathetic nerve functions in diabetic subjects with variable diabetic neuropathy.

RESEARCH DESIGN AND METHODS — Frequency domain analysis of 24-h Holter ECG was done for 132 diabetic subjects (84 without any symptomatic neuropathy; 37 with only symptomatic peripheral neuropathy; 11 with symptomatic autonomic neuropathy) and 57 normal volunteers to calculate the low frequency (LF) component representing the β-adrenoceptor function and the high frequency (HF) component representing the cardiac parasympathetic nerve function.

RESULTS — Cardiac LF and HF components in diabetic subjects without peripheral neuropathy showed values comparable to those of normal volunteers and a similar circadian rhythm. Diabetic subjects with peripheral neuropathy or autonomic neuropathy showed significantly depressed LF and HF components and loss of the circadian rhythm of LF and HF components compared with diabetic subjects without neuropathy. Impairment of the LF component in the afternoon could be accounted for by the duration of diabetes and elevated HbA_{1c} level. Impairment of the HF component at night could be accounted for by the duration of diabetes but not an elevated HbA_{1c} level.

CONCLUSIONS — These data indicated that diabetic subjects with peripheral neuropathy and diabetic subjects with symptomatic autonomic neuropathy, but not diabetic subjects without neuropathy, showed a marked decrease in cardiac sympathetic and parasympathetic nerve functions and loss of circadian rhythm.

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Depressed heart rate variability is considered to be related to the increased mortality in diabetic subjects with autonomic neuropathy (1–3). Computerized spectral analyses of beat-to-beat R-R internal variations on a continuous electrocardiogram (ECG) have provided information on both cardiac sympathetic nerve function as the low frequency (LF) component of heart rate variability and parasympathetic nerve function as the high frequency (HF) component (4–10). With this method, diabetic subjects with or without symptomatic autonomic neuropathy were shown to have impaired diurnal cardiac autonomic nerve function (11–14). However, only limited information is available on diabetic subjects without autonomic neuropathy.

In this study, we used frequency domain analysis of 24-h Holter ECG to evaluate diurnal cardiac sympathetic and parasympathetic nerve functions in diabetic subjects with and without symptomatic peripheral neuropathy.

RESEARCH DESIGN AND METHODS

Analysis of heart rate variability

Holter tapes were analyzed using a Marquette Laser SXP Holter analysis system (Marquette Electronics, Milwaukee, WI) to identify and label each QRS complex. After the computer had automatically detected and labeled each QRS complex, each data file was reviewed and edited by a physician (H.O.). Next, the labeled QRS data stream was moved via high-speed interface to a microcomputer, where the data were analyzed by a computer program and additional editing was done. Measurements of heart period variability were calculated and printed for the entire 24 h. Only 24-h recordings with >18 h of analyzable data were accepted for analysis. Each printout, including R-R intervals, was selected and measured.

Power spectral analysis of R-R intervals

To subtract the R-R interval from the Holter ECG record, 512 consecutive normal-normal intervals were depicted for each 15-min period (0800–0815, 0815–0830, etc.) from 0800 to 0800 of the next day. An autoregressive algorithm, previously described (7,15), was used for power spectral analysis of the R-R records. The model order was chosen to minimize Akaike's (16) final prediction error figure of merit after several iterations by increasing the order. The program provided the individual power and center frequency of each spectral component. We defined a sum of powers with the central frequency at 0.15–0.4 Hz (HF) as the respi-

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Abbreviations: DAN, diabetic subjects with symptomatic autonomic neuropathy; DNN, diabetic subjects without neuropathy; DPN, diabetic subjects with peripheral neuropathy; ECG, electrocardiogram; HF, high frequency; LF, low frequency; %LF, percentage low frequency component; TF, total frequency.

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

Table 1—*Patient characteristics*

	Subjects			
	Normal	DNN	DPN	DAN
n	57	84	37	11
Sex (M/F)	(35/22)	(56/28)	(23/14)	(7/4)
Age (years)	56.4 ± 1.3	55.8 ± 0.9	58.8 ± 1.4	47.5 ± 2.0*†‡
BMI (kg/m²)	22.7 ± 0.6	22.1 ± 0.6	22.2 ± 0.6	21.6 ± 1.2
Disease duration (years)	—	10.2 ± 0.9	15.9 ± 1.3†	14.3 ± 2.8
HbA_{1c} (%)	5.0 ± 0.02	8.4 ± 0.20*	8.7 ± 0.28*	9.7 ± 0.58*
Systolic blood pressure (mmHg)	126 ± 2.1	130 ± 2.0	134 ± 4.0	144 ± 8.3
Diastolic blood pressure (mmHg)	77 ± 6.0	75 ± 1.5	76 ± 2.3	84 ± 2.7
Total cholesterol (mmol/l)	5.6 ± 0.19	5.4 ± 0.12	5.4 ± 0.21	6.2 ± 0.26
HDL cholesterol (mmol/l)	1.5 ± 0.18	1.6 ± 0.15	1.3 ± 0.10	1.6 ± 0.22
Triglyceride (mmol/l)	1.3 ± 0.17	1.6 ± 0.09	1.5 ± 0.10	1.7 ± 0.15
CVrr (%)	4.1 ± 0.19	3.1 ± 0.09*	2.8 ± 0.06*	1.4 ± 0.10*†‡
NCV of median nerve (m/s)	58.3 ± 0.4	54.6 ± 0.3*	44.4 ± 0.4*†	43.8 ± 1.5*†
NCV of tibial nerve (m/s)	46.4 ± 0.4	44.8 ± 0.3*	34.8 ± 0.5*†	33.4 ± 1.0*†

Data are means ± SEM. *$P < 0.05$ vs. normal subjects; †$P < 0.05$ vs. DNN; ‡$P < 0.05$ vs. DPN. CVrr, coefficient variation of R-R intervals; NCV, nerve conduction velocity.

ratory sinus arrhythmia component (cardiac parasympathetic nerve function) (17) and a sum of powers with the central frequency at 0.03–0.15 Hz (LF) as the cardiac sympathetic nerve function (18). Total frequency (TF) was calculated as a sum of HF and LF. Percentile LF (%LF) was calculated as LF/TF and expressed as a percentage. In considering the R-R interval variation caused by each single component relative to the mean R-R interval, we normalized the magnitude of each component by dividing the square of mean R-R intervals as previously described (15). When one 15-min duration had two or more 512 consecutive normal-normal intervals, the LF and HF components were averaged separately. The TF component, LF component, HF component, and %LF were averaged for different time periods: 24 h (0800–0800), 0800–1200, 1200–1800, 1800–2400, 0000–0600, and 0600–0800.

Subjects

There were 132 subjects with type 2 diabetes aged 40–78 years and 57 normal subjects aged 40–78 years who volunteered to take part in the study (Table l). The definition of type 2 diabetes was based on World Health Organization criteria. All patients who fulfilled the following inclusion criteria were considered for the study: *1*) no episodes of ketoacidosis, *2*) diagnosis of diabetes after >30 years of age, and *3*) insulin therapy (if any) started after at least 5 years of known disease.

The patients were divided into three groups according to beat-to-beat variation in heart rate, blood pressure changes during

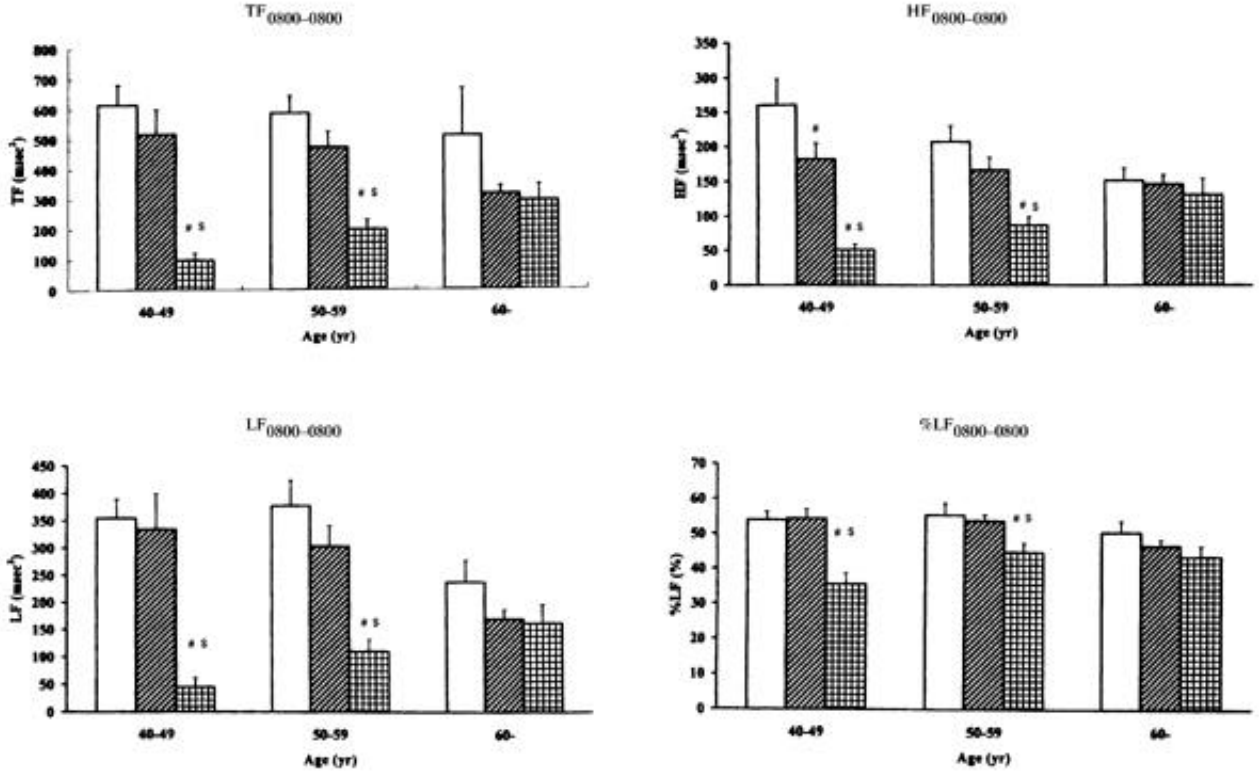

Figure 1—*TF component during 0800–0800 ($TF_{0800–0800}$), LF component during 0800–0800 ($LF_{0800–0800}$), HF component during 0800–0800 ($HF_{0800–0800}$), and %LF during 0800–0800 ($\%LF_{0800–0800}$) in normal subjects (□), diabetic subjects without neuropathy (▨), and diabetic subjects with peripheral neuropathy (▦) aged 40–49, 50–59, and 60 years old and more. #Statistical significance (P < 0.05) vs. normal subjects; $statistical significance (P < 0.05) vs. diabetic subjects without neuropathy. Data are means ± SEM.*

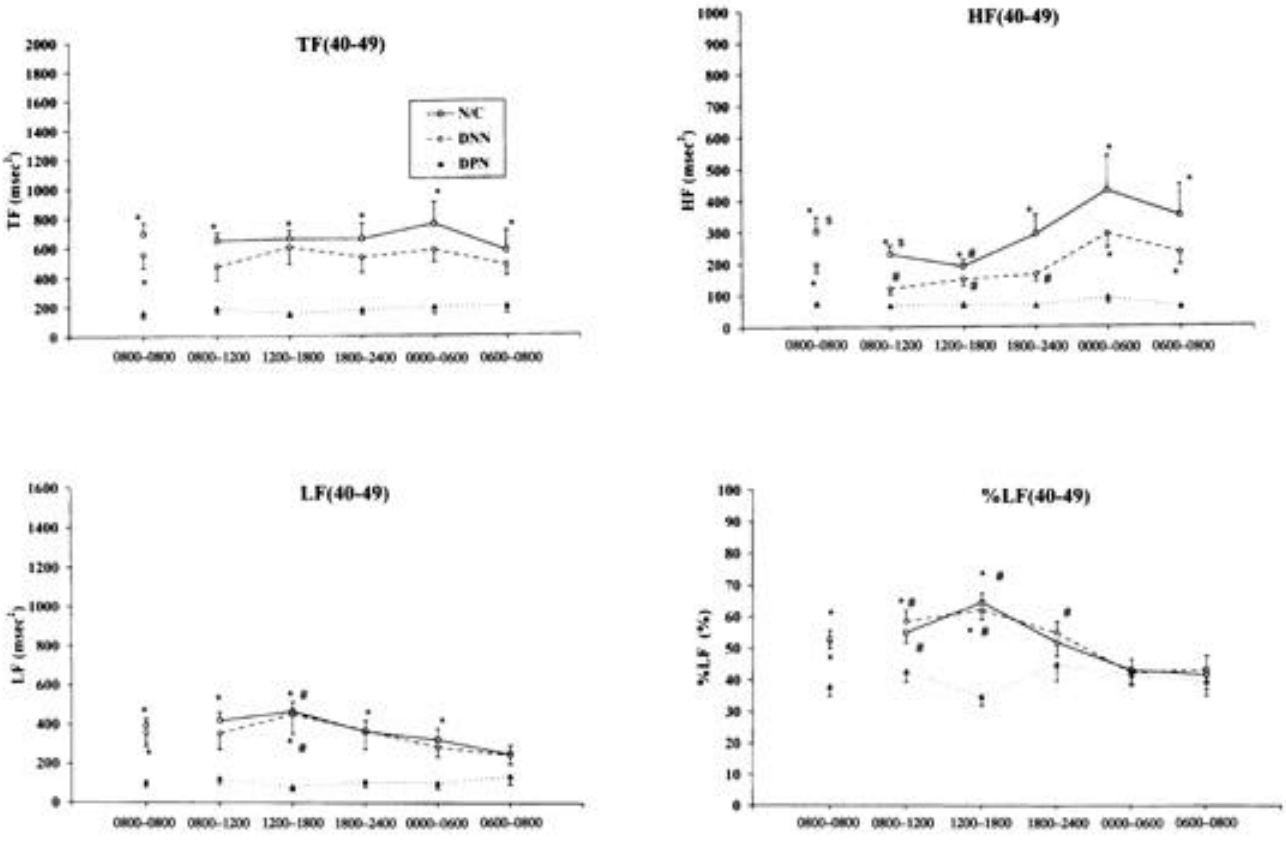

Figure 2—*TF, LF, HF, and %LF component during 0800–0800, 0800–1200, 1200–1800, 1800–2400, 0000–0600, and 0600–0800 in 40- to 49-year-old healthy volunteers (N/C) and the DPN and DNN groups. *Significant difference versus the value for the DPN group; #significant difference from values during 0000–0600. Data are means ± SEM.*

change of position from supine to standing, peroneal nerve conduction velocities, and clinical signs or symptoms of peripheral neuropathy (paresthesia, burning pains, decreased vibration sensation, absence of ankle reflex) and autonomic neuropathy (impotence, absence of sweat secretion on feet and legs, postural syncope, and bladder dysfunction). The first group was composed of diabetic subjects without neuropathy (DNN); they had normal beat-to-beat variation in heart rate (coefficient of variation of ECG R-R intervals >2.5%), normal orthostatic blood pressure response (decrease in systolic blood pressure <30 mmHg 1 min after standing up), normal median nerve conduction velocity (≥50 m/s), and normal tibial nerve conduction velocity (>40 m/s), with no clinical symptoms of peripheral or autonomic neuropathy. The second group was composed of diabetic subjects with peripheral neuropathy (DPN): patients having normal beat-to-beat variation of heart rate without clinical symptoms of autonomic neuropathy but having abnormal median nerve conduction velocity <50 m/s and abnormal tibial nerve conduction velocity <40 m/s with clinical symptoms of peripheral neuropathy. The third group was composed of diabetic subjects with symptomatic autonomic neuropathy (DAN): patients having reduced beat-to-beat variation of heart rate. All the patients showed orthostatic hypotension and at least one clinical symptom of autonomic neuropathy. The normal control group was composed of 57 healthy subjects aged 40–78 years. All except those aged ≥60 years were office workers. Routine laboratory and physical examinations were done to eliminate those with diabetes, cardiovascular diseases, and neurological disorders. Some of these healthy subjects had been evaluated in the previous study (15). Table 1 summarizes the clinical features of the patients. None of the subjects were taking β-blockers or anti-arrhythmia drugs or digitalis. The patients with symptomatic autonomic neuropathy (DAN, *n* = 11) were compared with age-matched normal subjects (*n* = 17) and both age-matched and duration-matched patients without diabetic neuropathy (*n* = 11) or patients with peripheral neuropathy (*n* = 8) from the normal and diabetic subjects.

The absence of chronic heart failure was confirmed by careful physical examination, resting ECG, and chest X-ray examination. No subject had had any episode of myocardial infarction or ECG findings of old myocardial infarction. Peripheral nerve function was evaluated by temperature-controlled nerve conduction velocity in the median nerve on one side. From the consecutive 100 normal R-R intervals on the ECG recorded after 5 min of bed rest, mean and SD of these R-R intervals were calculated to get a coefficient of variation of 100 × SD/mean.

Statistical analysis

All data are shown as mean ± SEM. Statistical difference was evaluated by one-way analysis of variance. Multivariant forward and backward regression analysis was used to detect the significant clinical risk factor for impairment of cardiac autonomic nervous function.

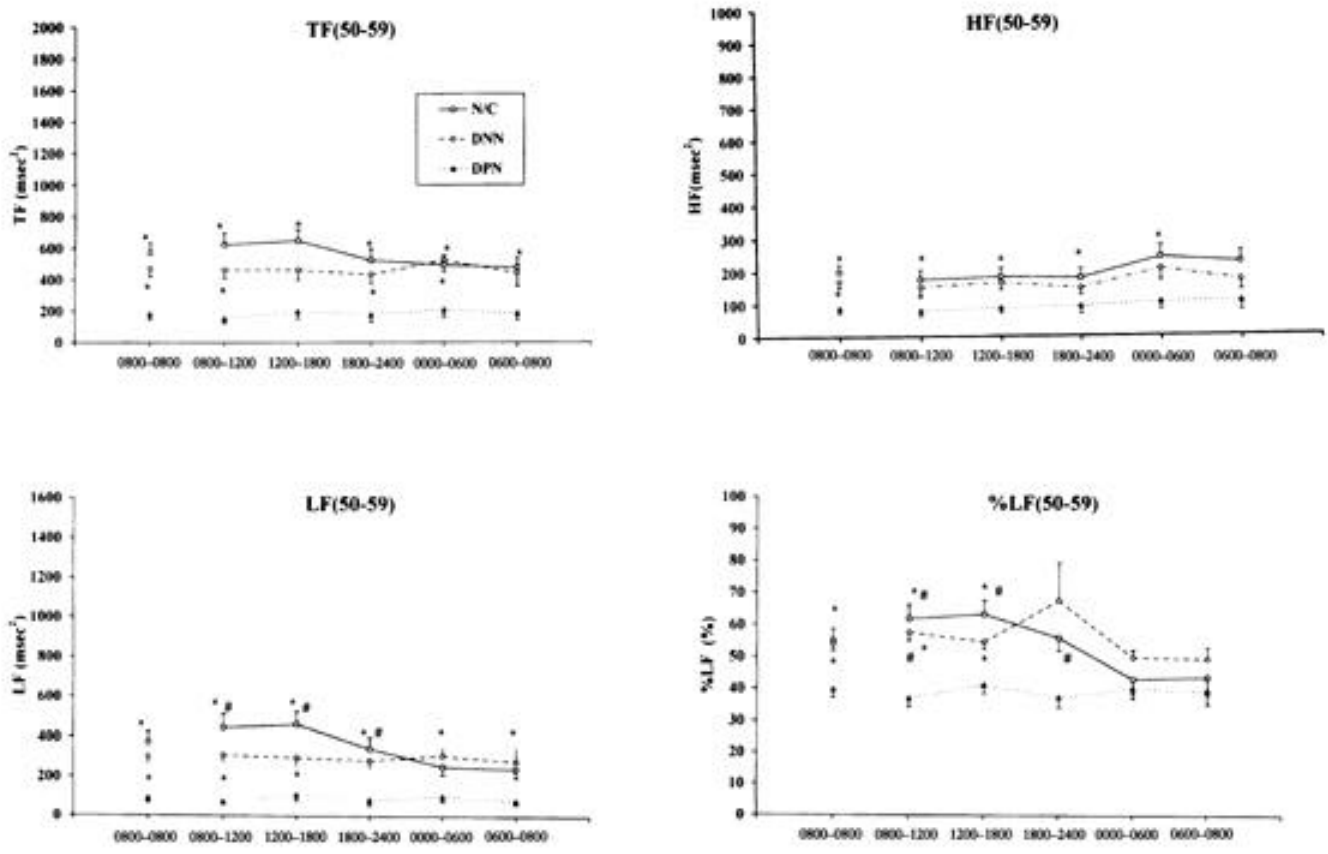

Figure 3—*TF, LF, HF, and %LF component during 0800–0800, 0800–1200, 1200–1800, 1800–2400, 0000–0600, and 0600–0800 in 50- to 59-year-old healthy volunteers (N/C) and the DPN and DNN groups. *Significant difference versus the value for the DPN group; #significant difference from values during 0000–0600. Data are means ± SEM.*

RESULTS — The central frequencies of LF and HF components showed no significant differences among the normal subjects (0.096 ± 0.001 and 0.289 ± 0.001 Hz), the DNN group (0.096 ± 0.001 and 0.293 ± 0.001 Hz), the DPN group (0.097 ± 0.001 and 0.293 ± 0.001 Hz), and the DAN group (0.092 ± 0.007 and 0.284 ± 0.005 Hz). The LF and HF component averaged for 24 h in the DNN group showed comparable values with normal volunteers and decreased in an age-dependent fashion, as found for the normal subjects, except the HF component of those in the DNN group aged 40–49 years. The ratio of the LF component in the TF component ($\%LF_{0800–0800}$) showed a consistent value in individuals in the DNN group aged 40 years. Individuals in the DPN group aged 40–49 years and 50–59 years showed significantly depressed LF and HF components in comparison with normal volunteers and diabetic subjects without neuropathy. The $\%LF_{0800–0800}$ was significantly lower than that in the normal subjects and the DNN group (Fig. 1). Individuals in the DPN group aged 60 years showed LF and HF components comparable with the normal subjects and individuals in the DNN group aged 60 years. The $\%LF_{0800–0800}$ was also comparable with that in the normal subjects and individuals in the DNN group aged 60 years (Fig. 1).

In individuals in the DNN group aged 40–49 years, the LF component peaked during 1200–1800 and then gradually decreased to the nadir during 0600–0800. The LF $component_{1200–1800}$ was significantly higher than the LF $component_{0000–0600}$. The HF component showed its nadir during 1200–1800 and then gradually increased to its peak during 0000–0600. The HF $component_{0800–1200}$, HF $component_{1200–1800}$, and HF $component_{1800–2400}$ were significantly lower than the HF $component_{0000–0600}$. Thus, the %LF showed its peak during 1200–1800 and then gradually decreased to the nadir during 0000–0600 (Fig. 2). A similar diurnal profile of LF and HF components was observed for normal subjects aged 40–49 years (Fig. 2) and 50–59 years (Fig. 3). No diurnal profile of LF and HF components was observed for individuals in the DNN group aged 50–59 years (Fig. 3) and in the DPN group aged 40–49, 50–59, and 60 years.

The TF $component_{0800–0800}$, LF $component_{0800–0800}$, HF $component_{0800–0800}$, and $\%LF_{0800–0800}$ of the DAN group were significantly lower than those of age-matched individuals in the DNN group and normal subjects, but not significantly lower than that of age-matched individuals in the DPN group. The DAN group showed complete loss of circadian LF component, HF component, and %LF rhythms compared with those of age-matched individuals in the DNN group and age-matched normal subjects (Fig. 4).

Multivariant regression analysis was carried out to elucidate the risk factors in the impairment of cardiac autonomic nerve function. For the LF component in the afternoon, the duration of diabetes and elevated HbA_{1c} level were contributing factors. However, for the HF component at night, the factors were duration of diabetes and elevated diastolic blood pressure but not HbA_{1c} level (Table 2).

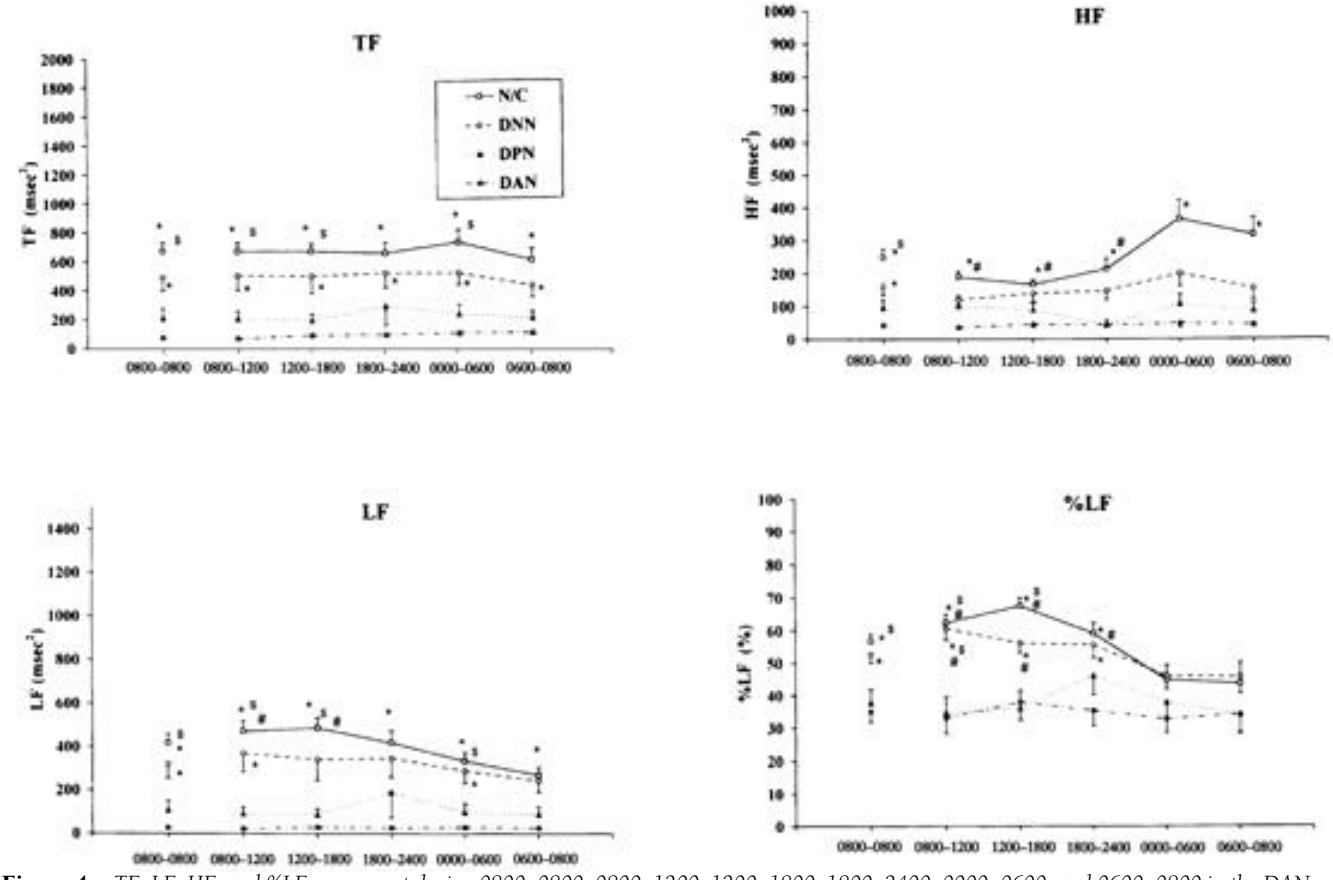

Figure 4—*TF, LF, HF, and %LF component during 0800–0800, 0800–1200, 1200–1800, 1800–2400, 0000–0600, and 0600–0800 in the DAN group, age- and duration-matched individuals in the DPN and DNN groups, and age-matched healthy volunteers (N/C). *Significant difference versus the value for individuals in the DAN group; $significant difference versus the value for individuals in the DPN group; #significant difference from values during 0000–0600. Data are means ± SEM.*

CONCLUSIONS — Diabetic subjects with autonomic neuropathy are known to display high mortality (1,2), and cases of sudden death have also been reported (2,3). In this study, frequency domain analysis of whole-day heart rate variability was used to assess the diurnal changes in sympathovagal control of heart rate in diabetic subjects with and without clinical autonomic neuropathy. Diabetic subjects with symptomatic autonomic neuropathy showed markedly and significantly impaired whole-day LF

Table 2—*Multivariant regression analysis on cardiac autonomic nerve function of diabetic subjects*

	TF component$_{0800–0800}$			LF component$_{1200–1800}$			HF component$_{0000–0600}$		
	Univariant correlation coefficient	Partial correlation coefficient	*F* value	Univariant correlation coefficient	Partial correlation coefficient	*F* value	Univariant correlation coefficient	Partial correlation coefficient	*F* value
Age	−0.164	—	—	−0.191	—	—	−0.102	—	—
Sex	0.130	—	—	0.067	—	—	−0.029	—	—
BMI	−0.056	—	—	−0.068	—	—	−0.031	—	—
Disease duration	−0.263	−0.238	6.24*	−0.270	−0.226	4.64*	−0.345	−0.302	8.23*
HbA_{1c}	−0.295	−0.255	5.22*	−0.244	−0.192	3.35*	−0.249	—	—
Systolic blood pressure	−0.207	—	—	−0.165	—	—	−0.182	—	—
Diastolic blood pressure	−0.110	—	—	−0.057	—	—	−0.142	−0.173	2.71*
Total cholesterol	−0.146	—	—	−0.130	—	—	0.005	—	—
HDL cholesterol	0.044	—	—	−0.071	—	—	−0.047	—	—
Triglyceride	−0.077	−0.153	2.25	−0.007	—	—	−0.032	—	—
R^2		0.1496			0.1078			0.1474	

Multivariant regression analyses were done on 132 subjects with type 2 diabetes. *$P < 0.05$. Sex: men = 1, women = 0.

and HF components compared with age-matched and duration-matched diabetic subjects without peripheral neuropathy. Also, they showed loss of the circadian rhythm of the cardiac autonomic nerve function. These observations well matched studies on diabetic subjects with or without autonomic neuropathy (12–14).

Diabetic subjects without neuropathy aged 40–49, 50–59, and 60 years showed comparable LF and HF components for all time durations in comparison with those of age-matched normal volunteers. On the other hand, diabetic subjects with peripheral neuropathy aged 40 years or more showed significantly lower LF and HF components than age-matched diabetic subjects without peripheral neuropathy did. Concerning the circadian rhythm of cardiac sympathetic and parasympathetic nerve functions, diabetic subjects without neuropathy aged 40–49 years showed similar circadian LF and HF components to those in normal subjects. On the other hand, diabetic subjects with symptomatic peripheral neuropathy aged 40 years showed loss of normal circadian rhythm of the cardiac autonomic nerve function—the pattern being quite similar to those of diabetic subjects with symptomatic autonomic neuropathy. This phenomenon might be comparable with the reduced sympathetic nerve activity in type 1 diabetes before overt autonomic neuropathy (20).

Together with the decrease in the power spectral density of LF and HF components, these data suggest that diabetic subjects with peripheral neuropathy show the existence of impaired cardiac autonomic nerve function. However, diabetic subjects with peripheral neuropathy are not reported to display a high mortality rate comparable to diabetic subjects with autonomic neuropathy. Whether some additional mechanism(s) leads to symptoms of autonomic neuropathy and the high mortality remains to be clarified.

In this study, multivariant analysis was done to elucidate possible risk factors to explain the impairment of cardiac sympathetic and parasympathetic nerve functions in diabetic subjects. Elevated HbA_{1c} level and duration of diabetes were found to be independent risk factors for impaired LF component. This phenomenon is comparable with the inverse relationship between autonomic nerve function and HbA_{1c} level in subjects with type 2 diabetes (8) and type 1 diabetes (11). Because short-term poor glycemic control may affect HbA_{1c} level, it may also affect cardiac sympathetic nerve function. To test this hypothesis, evaluation of cardiac sympathetic nerve function must be done before and after short-term glycemic control in diabetic subjects.

In conclusion, we have shown that the diurnal profile of cardiac autonomic nerve function is impaired in diabetic subjects with symptomatic peripheral neuropathy. Further, follow-up spectral analysis of R-R variability might elucidate the natural progression of autonomic neuropathy in diabetic patients.

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