Reversed Circadian Blood Pressure Rhythm Is Associated With Occurrences of Both Fatal and Nonfatal Vascular Events in NIDDM Subjects

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To assess the significance of reversed circadian blood pressure (BP) rhythms as a predictive factor of vascular events in NIDDM, vital status after an average 4-year follow-up was determined in 325 NIDDM subjects in whom the circadian BP profile had been monitored between 1988 and 1996. Circadian BP rhythm was analyzed by the COSINOR (a compound word for cosine and vector) method, as previously described. After exclusion of 37 dropped-out subjects, 288 were recruited to the further analysis, of which 201 had a normal circadian BP rhythm (group N) and the remaining 87 had a reversed one (group R). There was no difference in sex, HbA_{1c}, the prevalence of smokers, serum lipids, or serum electrolytes between groups N and R at baseline, whereas age, the prevalence of hypertension, serum creatinine, and diabetic complications were more pronounced in group R than in group N. During the follow-up period (which averaged 52 months in group N and 36 months in group R), fatal and nonfatal vascular (cerebrovascular, cardiovascular, peripheral vascular arteries, and retinal artery) events occurred in 20 subjects in group N and 56 in group R. Unadjusted survival times and event-free times were estimated by the Kaplan-Meier product-limit method, and there was a significant difference in both unadjusted survival and event-free survival rates between groups N and R ($P < 0.001$ each; log-rank test). The Cox proportional-hazards model adjusted for age, sex, circadian BP pattern, duration of diabetes, therapy for diabetes, various diabetic complications, and hypertension demonstrated that circadian BP pattern and age exhibited significant, high adjusted relative risks for fatal events, and that diabetic nephropathy, postural hypotension, and hypertension as well as circadian BP pattern exhibited significant, high adjusted relative risks with respect to the occurrence of various nonfatal vascular events. These results suggest that reversed circadian BP rhythm is associated with occurrences of both fatal and nonfatal vascular events in NIDDM subjects. ***Diabetes*** **47:1501–1506, 1998**

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BP, blood pressure; mBP, mean blood pressure.

NIDDM subjects have higher morbidity and mortality for various vascular events than do those in the general population in Japan (1–3) and other countries (4–7). Cerebro-cardiovascular and renal diseases related to the progression of atherosclerosis are well known to be the most frequent causes of death (1–10). Furthermore, poor glycemic control, onset at younger age, hypertension, hyperlipidemia, and progressed diabetic microangiopathy are demonstrated as risk factors for vascular events in diabetic subjects (1–10), making it crucial to control these risk factors to prevent various vascular events.

In recent years, ambulatory blood pressure (BP) measurement has been shown to be more useful in evaluating the progression of diabetic microvascular complications than casual or office BP measurements, because of its reproducibility, prediction of target organ damage, and exclusion of the "white coat" phenomenon (11–15).

We previously reported that NIDDM subjects were largely divided into two groups according to circadian BP profiles: one was a diabetic group with a normal circadian BP rhythm and the other was a diabetic group with a reversed one. That reversal of circadian BP rhythm may be related to postural hypotension and/or advanced diabetic nephropathy (16). However, long-term follow-up studies for NIDDM subjects in relation to circadian BP rhythms are sparse, so that the prognostic significance of the ambulatory BP pattern is not clear (17). In this study, we followed up NIDDM subjects with normal and reversed circadian BP rhythms, examined their prognoses, and determined the predictive factors of various fatal and nonfatal vascular events.

RESEARCH DESIGN AND METHODS

Subjects. The subjects studied were 325 NIDDM subjects (207 men, 118 women) who were initially admitted to the Kanazawa Medical University Hospital from December 1988 to November 1996 and then followed in our outpatient clinic. Informed consent was obtained from each participant. NIDDM was diagnosed according to the criteria of the World Health Organization (18). These diabetic subjects were carefully questioned and examined. They were defined as those without any history of various vascular complications: ischemic cardiac, cerebral, and peripheral vascular diseases, congestive heart failure, renal failure, and other events in which diabetes could play a contributory role. During the follow-up period, a total of 37 subjects were lost to follow-up, including subjects who died of causes unrelated to diabetes: 11 cancer, 1 pneumonia, 1 traffic accident, 1 suicide, 4 unknown. Of the 325 NIDDM subjects, 288 entered into the study.

Methods. Diabetic complications in each subject were evaluated on the first admission, as previously described (16). Briefly, the diagnosis of retinopathy was made by ophthalmoscopy, and fluorescein angiography was performed by experienced ophthalmologists in our university. Retinopathy was divided into four stages: none, sim-

TABLE 1
Clinical and biochemical characteristics of diabetic subjects with normal and reversed circadian BP rhythms at entry

	Diabetic subjects		
	With a normal circadian BP rhythm	With a reversed circadian BP rhythm	*P* value
n	201	87	—
Follow-up period (months)	51.5 ± 28.0	36.0 ± 26.7	<0.05
Age at entry (years)	52.3 ± 14.1	57.0 ± 13.0	<0.01
Sex (M/F)	133/68	51/36	NS*
BMI (kg/m^2)	24.2 ± 4.5	23.0 ± 3.5	<0.01
Diabetic subjects with hypertension	62 (30.8)	43 (49.4)	<0.01*
Current smokers	73 (36.3)	36 (41.4)	NS*
Duration of diabetes (years)	6.1 ± 6.4	9.5 ± 6.0	<0.01
Treatment for diabetes (diet alone/OH/insulin)	92/71/38	19/22/46	<0.001*
HbA_{1c} (%)	8.7 ± 2.4	9.2 ± 2.8	NS
Serum total cholesterol (mmol/l)	5.12 ± 1.17	5.27 ± 1.41	NS
Serum triglyceride (mmol/l)	1.69 ± 1.31	2.02 ± 1.68	NS
Serum HDL cholesterol (mmol/l)	1.42 ± 0.48	1.39 ± 0.53	NS
Serum total protein (g/l)	65 ± 5.5	64 ± 7.7	NS
Serum sodium (mmol/l)	142 ± 2.2	140 ± 3.3	NS
Serum potassium (mmol/l)	4.0 ± 0.4	4.1 ± 0.5	NS
Serum creatinine (μmol/l)	76.0 ± 28.3	96.4 ± 60.1	<0.01
Urinary sodium (mmol/day)	127 ± 51	128 ± 67	NS
Urinary potassium (mmol/day)	38.9 ± 14.1	41.5 ± 22.6	NS
Glomerular filtration rate (ml/s)	1.54 ± 0.42	1.30 ± 0.46	<0.01

Data are means ± SD, *n*, or *n* (%). OH, oral hypoglycemics. *Determined by χ^2 test.

ple, preproliferative, and proliferative. Somatic neuropathy was defined as reduced tendon reflexes, especially the Achilles and patellar reflexes, and abnormal electrodiagnostic studies. Cardiovascular autonomic dysfunction was estimated by measuring orthostatic BP and heart rate changes (within 10 min after assuming the upright position) and the coefficient of variation of R-R intervals (CVR-R) during deep breathing (6 times/min at a heart rate of 100) (19). Nephropathy was divided into three stages according to urinary albumin excretion rates: nil nephropathy (normoalbuminuria, <15 μg/min), incipient nephropathy (microalbuminuria, 15–200 μg/min), and overt nephropathy (macroalbuminuria, >200 μg/min).

Ambulatory 24-h mean BP (mBP; oscillometric mode) recordings were performed under regular hospital conditions, as previously described (16). None of the diabetic subjects took any medication for at least 1 week before the ambulatory BP monitoring except for oral hypoglycemic agents or insulin. MBP readings were taken every 20 min from 0500 to 2200 and every hour from 2200 to 0500. The time series data for mBP were analyzed by the COSINOR (cosine and vector) method of Halberg et al. (20). Abnormal or reversed circadian BP rhythm was defined as the acrophase of mBP distributed between 2000 and 0800 (16).

After ambulatory 24-h mBP measurements, antihypertensive treatment was initiated when BP exceeded 160/95 mmHg on three consecutive occasions during the admission or after release to our outpatient clinic. The antihypertensive drugs—long-acting calcium channel blockers, ACE inhibitors, α_1-blockers, and diuretics—were usually given either alone or in various combinations, and the choice of these drugs was adjusted when necessary at every visit. β-Blockers were not used in this study because of their well-known inhibitory effects on insulin secretion and insulin sensitivity.

As end points, various fatal and nonfatal vascular events considered to be diabetes-related were determined. Cerebrovascular events were divided into cerebral infarction and hemorrhage using emergent brain computed tomography (CT) scan. Clinical diagnoses were made for subjects with ischemic heart disease (angina pectoris or acute myocardial infarction), a peripheral vascular event (diabetic gangrene), and retinal lesions. Congestive heart failure was given as a cause for the fatal or nonfatal vascular events when the subject showed orthopnea, raised jugular venous pressure, bibasalar crackles, pulmonary venous hypertension, and/or interstitial edema on chest X ray. End-stage renal failure and introduction of hemodialysis were also counted as a nonfatal vascular event.

Serum and urinary concentrations of sodium, potassium, and creatinine and serum total protein and lipids were measured on a sequential multiple analyzer plus computer (Technicon, New York). Urinary albumin was determined with a Latex agglutination nephelometric immunoassay kit (Eiken, Tokyo, Japan). HbA_{1c} was measured by the chromatographic method with a hemoglycosimeter auto-A_{1c}-TM (Daiichi, Kyoto, Japan).

Statistical analysis. Data are presented as means ± SD. As all data for the comparison of group means were almost normally distributed, Student's *t* test was applied for data with equal variances; otherwise, Welch's test was applied for data with nonequal variances. For testing of the number of subjects in two groups, the χ^2 test was used. If three or more graded data were present, Wilcoxon's rank-sum test was appropriately used. *F* test was applied to statistical analysis of a cosine function in the COSINOR method. Although the analysis included only the first event for subjects who died or experienced nonfatal vascular events, the analysis for nonfatal events was done after the exclusion of deceased subjects. Survival and event-free survival curves were estimated using the Kaplan-Meier product-limit method and compared by the log-rank test. Unadjusted relative risks were obtained from the Cox-Mantel's test. The effects of prognostic factors on survival and the occurrence of various vascular events were evaluated by the Cox proportional-hazards model. In this analysis, dummy variables were used for sex (male or female), circadian BP pattern (normal or reversed), treatment for diabetes (diet alone, diet plus oral hypoglycemic agents, or diet plus insulin), and BP levels (normotensive or hypertensive). Graded data for diabetic retinopathy and nephropathy were treated as graded numbers, and the other measured data were treated as continuous variables. Relative risks adjusted for age, sex, duration of diabetes, treatment for diabetes, hypertension, and various microvascular complications for fatal and nonfatal vascular events in the Cox's model were calculated as the antilogarithm of the bi-coefficient (e^{bi}). The 95% CIs around the adjusted relative risk estimate were obtained from the formula $e^{(bi \pm 2 \times SEbi)}$, where SEbi is the standard error of bi. The statistical significance was defined as a two-tailed *P* value < 0.05.

RESULTS

Clinical and biochemical characteristics and diabetic microvascular complications in the diabetic subjects at entry. Complete follow-up data were obtained from 288 (88.6%) of the 325 subjects who entered the study. Of the 288 subjects, 201 (69.8%) had a normal circadian BP rhythm and the remaining 87 (30.2%) had a reversed one. Mean follow-up periods in diabetic subjects with normal and reversed circadian BP rhythms were 51.5 ± 28.0 months (range 1–95 months) and 36.0 ± 26.7 months (range 1–93 months), respectively. Clinical and biochemical characteristics in these two diabetic groups are shown in Table 1. Although there was no

TABLE 2
Microvascular complications in diabetic subjects with normal and reversed circadian BP rhythms

	Diabetic subjects		
	With a normal circadian BP rhythm	With a reversed circadian BP rhythm	*P* value
n	201	87	—
No complications	129 (58.1)	8 (9)	<0.001*
Neuropathy			
Somatic neuropathy	89 (40.1)	77 (89)	<0.001*
Autonomic neuropathy			
Postural hypotension			
Fall in systolic BP (mmHg)	–3.1 ± 8.7	–18.6 ± 12.3	<0.01
Increase in heart rate (beats/min)	24.7 ± 8.9	17.2 ± 9.1	<0.01
CVR-R during deep breathing (%)	4.02 ± 2.02	2.36 ± 1.25	<0.01
Retinopathy			
No retinopathy	137 (68)	12 (14)	—
Simple retinopathy	26 (13)	22 (25)	<0.001†
Preproliferative retinopathy	28 (14)	26 (30)	—
Proliferative retinopathy	10 (5)	27 (31)	—
Nephropathy			
Nil nephropathy	130 (65)	19 (22)	—
Microalbuminuria	52 (26)	30 (34)	<0.001†
Macroalbuminuria	19 (9)	38 (44)	—

Data are means ± SD or *n* (%). CVR-R, coefficient of variation of R-R intervals during deep breathing. *Determined by χ^2 test; †determined by Wilcoxon's rank-sum test.

difference in sex between these two groups, there was a significant difference in age, BMI, the prevalence of hypertension, duration of diabetes, treatment for diabetes, serum creatinine level, and glomerular filtration rate. The values of HbA_{1c}, serum lipids, serum total protein, and serum and urinary electrolytes and the prevalence of current smokers did not differ significantly between the two diabetic groups.

A comparison of diabetic microvascular complications in the two diabetic groups is shown in Table 2. All diabetic microvascular complications were more pronounced in diabetic subjects with a reversed circadian BP rhythm than in those with a normal one**.** However, none of the diabetic subjects had reached end-stage renal failure at the time when the ambulatory BP monitoring was performed.

Twenty-four–hour mBP profiles in diabetic subjects with normal and reversed circadian mBP rhythms. Twenty-four–hour profiles of mBP in diabetic subjects with and without fatal and nonfatal events are shown in Fig. 1*A* and *B*. When cosine curves analyzed by the COSINOR method were fitted against hourly mean values of mBP, all cosine curves were statistically significant ($P < 0.001$ each, *F* test). The levels of circadian BP variability in diabetic subjects with fatal and nonfatal events were higher than in survived or event-free diabetic subjects, irrespective of circadian BP pattern.

Survival analysis in diabetic subjects with normal and reversed circadian BP rhythms. Vascular events were observed in 76 cases, 31 fatal and 45 nonfatal. Fatal vascular events in diabetic subjects with normal and reversed circadian BP rhythms included congestive heart failure in 3 and 11, cerebral infarction in 2 and 8, cerebral hemorrhage in 1 and 2 (1 of 2 occurred at night), and sudden death in 0 and 4 (all 4 in the early morning), respectively. Of the 11 subjects with a reversed circadian BP rhythm who died of cardiac failure, 4 had commenced

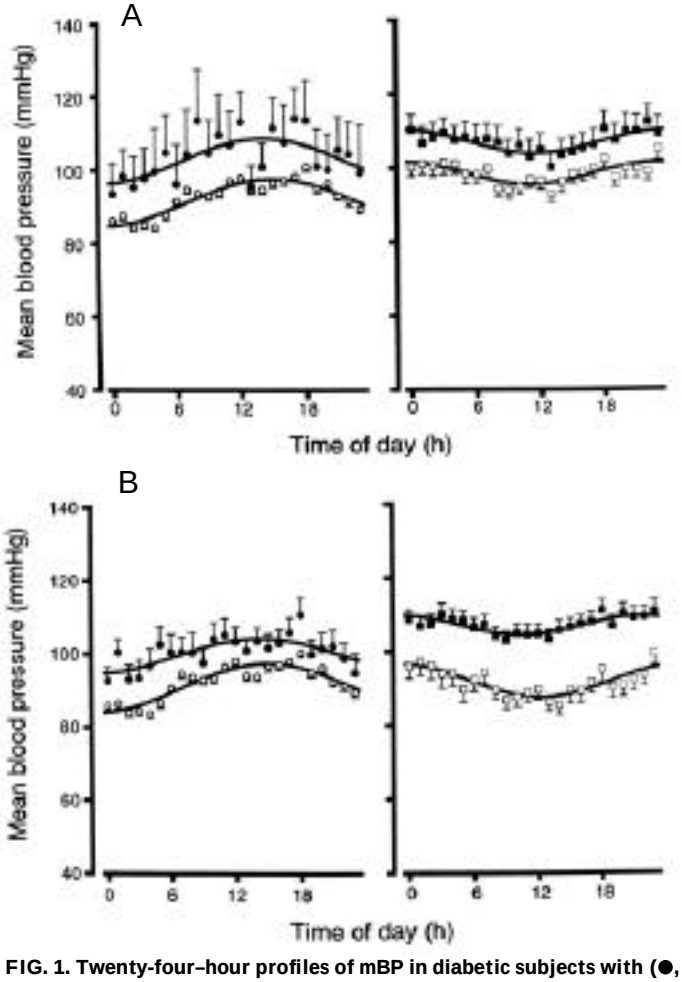

FIG. 1. Twenty-four–hour profiles of mBP in diabetic subjects with (●, ■) and without (○, □) fatal vascular events (*A*) and nonfatal vascular event (*B*). Left panels show those with a normal circadian BP rhythm, and right panels show those with a reversed circadian BP rhythm.

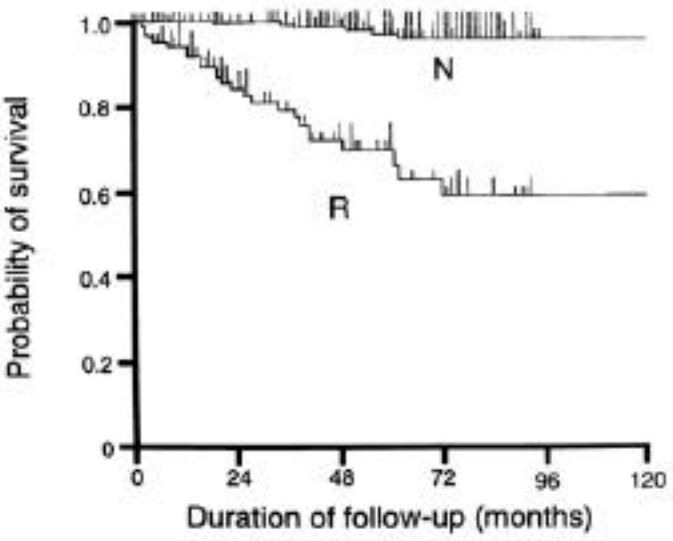

FIG. 2. Survival curves of diabetic subjects with normal (N) and reversed (R) circadian BP rhythms. The unadjusted relative risk for diabetic subjects with a reversed circadian BP rhythm was 20.6-fold higher than that of subjects with a normal rhythm ($P < 0.001$; Cox-Mantel's test).

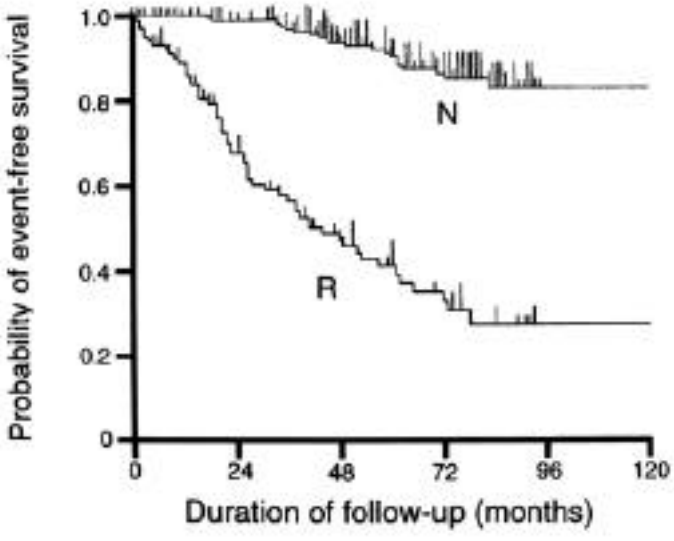

FIG. 3. Event-free survival curves of diabetic subjects with normal (N) and reversed (R) circadian BP rhythms. The unadjusted relative risk for diabetic subjects with a reversed circadian BP rhythm was 12.9-fold higher than that of subjects with a normal rhythm ($P < 0.001$; Cox-Mantel's test).

hemodialysis. Kaplan-Meier survival curves of diabetic subjects with normal and reversed circadian BP rhythms showed a significant difference in the survival rate (χ^2 = 51.56, $P < 0.001$; log-rank test, Fig. 2).

Nonfatal vascular events in diabetic subjects with normal and reversed circadian BP rhythms included renal failure requiring hemodialysis in 6 and 16, congestive heart failure in 1 and 3, angina pectoris in 1 and 1, acute myocardial infarction in 0 and 2, cerebral infarction in 2 and 2, diabetic gangrene in 0 and 1, vitreous hemorrhage in 4 and 5 (3 of 5 noted at awakening), and massive nasal hemorrhage at midnight in 0 and 1, respectively. The Kaplan-Meier plot of diabetic subjects with normal and reversed circadian BP rhythm showed a significant difference in event-free survival rate ($\chi^2 = 51.42$, $P < 0.01$; log-rank test, Fig. 3).

Factors predicting fatal and nonfatal vascular events in diabetic subjects studied. In the Cox proportional-hazards model, the adjusted relative risks for all factors listed for fatal events are shown in Table 3. Although there were significant differences in age, incidence of hypertension, duration of diabetes, treatment for diabetes, and microvascular complications between the two diabetic groups at baseline, age and circadian BP patterns exhibited a statistically significant adjusted relative risk for fatal events ($P < 0.05$ for each; Table 3).

Relative risks for nonfatal events, adjusted for the same variables used for fatal events in the Cox model, are also

TABLE 3
Adjusted relative risks for fatal and nonfatal events in diabetic subjects studied

	Factors for fatal events		Factors for nonfatal events	
	Adjusted relative risk (95% CI)	*P* value	Adjusted relative risk (95% CI)	*P* value
Circadian BP pattern	10.61 (1.55–72.79)	0.014	4.14 (1.68–10.22)	0.002
Age	1.06 (1.01–1.12)	0.020	1.01 (0.98–1.04)	0.412
Sex	0.59 (0.18–1.92)	0.355	1.34 (0.67–2.67)	0.399
Duration of diabetes	1.04 (0.94–1.14)	0.444	1.03 (0.97–1.09)	0.369
Treatment for diabetes				
Oral hypoglycemics*	1.91 (0.09–41.2)	0.673	0.94 (0.31–2.85)	0.907
Insulin*	4.54 (0.58–99.87)	0.328	1.11 (0.35–3.58)	0.857
Hypertension	4.74 (0.58–26.36)	0.069	4.18 (1.67–10.46)	0.002
Diabetic neuropathy				
Somatic neuropathy	3.66 (0.17–80.85)	0.402	1.59 (0.32–5.88)	0.475
Autonomic neuropathy				
Postural hypotension				
Fall in systolic BP	1.01 (0.95–1.09)	0.583	2.02 (1.98–3.06)	0.036
Increase in heart rate	0.99 (0.92–1.08)	0.935	1.00 (0.96–1.05)	0.949
CVR-R	0.51 (0.22–12.14)	0.121	0.95 (0.44–1.12)	0.436
Diabetic retinopathy	0.96 (0.45–2.06)	0.910	1.21 (0.80–1.83)	0.356
Diabetic nephropathy	0.85 (0.27–2.67)	0.780	2.34 (1.70–4.59)	0.038

CVR-R, coefficient of variation of R-R intervals during deep breathing. *Adjusted relative risks compared with that of diet alone.

shown in Table 3. In this analysis, hypertension, postural hypotension, and diabetic nephropathy, as well as circadian BP pattern, showed a statistically significant adjusted relative risk for nonfatal events ($P < 0.05$ for each).

DISCUSSION

Diabetic control, obesity, smoking, and hyperlipidemia in diabetic subjects may be major risk factors, probably in relation to the progression of atherosclerosis (2). These risk factors showed no statistical differences between diabetic subjects with normal and reversed circadian BP rhythms at entry in this study. Mean levels of BMI also were within normal limits in the two diabetic groups. These vascular risk factors, therefore, cannot fully account for the poorer prognosis in the diabetic subjects with a reversed circadian BP rhythm. Age is generally demonstrated to be related to the occurrence of fatal events (2,3,5). In this study, age adjusted for the other factors was not a risk factor for the occurrence of nonfatal vascular events, suggesting that reversal of circadian BP rhythm is not solely dependent on age. It is necessary to explore the significance of circadian BP pattern as an additional factor predicting mortality and morbidity among diabetic subjects. Accordingly, we further evaluated the effects of circadian BP pattern and diabetes-specific factors—duration of diabetes, treatment for diabetes, hypertension, and various microvascular complications—in addition to age and sex on the occurrence of fatal and nonfatal vascular events during an average 4-year follow-up.

In this follow-up study, we clearly demonstrated that diabetic subjects with a reversed circadian BP rhythm showed higher mortality and morbidity for various vascular events than did those with a normal rhythm. The predictive factors for fatal events analyzed by the Cox model were circadian BP pattern and age, whereas those for nonfatal events were hypertension, postural hypotension, and diabetic nephropathy, as well as circadian BP pattern. These results suggest that circadian BP pattern is more powerful for predicting fatal events than the other factors listed in Table 3 and that the presence of microvascular complications such as postural hypotension and nephropathy, even in normotensive diabetic subjects, is not only related to reversal of circadian BP rhythm (16), but is also a useful predictor for various nonfatal vascular events. Moreover, our results show that the presence of hypertension in diabetic subjects may potentially affect the prognosis. Thus, our results obtained from the Cox model demonstrate that the prognosis of diabetic subjects with a reversed circadian BP rhythm may not be worse simply because they had a longer duration of diabetes, a higher prevalence of insulin treatment, or more advanced microvascular complications than did those with a normal rhythm. Accordingly, the reversal of circadian BP pattern could not be only an epiphenomenon associated with advanced microvascular complications. Although above-mentioned risk factors in diabetic subjects are largely similar to the results of prospective population-based studies previously reported in Japan (1–3) and other countries (4–10), this is the first report indicating a significant association between the reversed circadian BP rhythm and occurrences of both fatal and nonfatal vascular events from a long-term retrospective study in NIDDM subjects. In a relatively short follow-up study, Liniger et al. (17) reported higher fatal and nonfatal vascular events in diabetic subjects with abnormal cardiovascular reflexes and a nocturnal BP rise than in those with a pronounced BP fall at night. Most of their diabetic subjects who showed a nocturnal rise in BP also had massive proteinuria. Abnormal cardiovascular reflex, especially postural hypotension, could be responsible for volume retention resulting from an impairment of renal water and electrolyte excretion (21). An increase in urinary albumin excretion was also correlated with a decrease in nocturnal BP fall (22) and an impairment of autonomic dysfunction (23). Thus, the progression of diabetic nephropathy and/or postural hypotension may lead not only to a rise in the levels of diurnal and nocturnal BPs but also to a reversed circadian BP rhythm through volume retention during the daytime, thereby resulting in the poorer prognosis for vascular events in diabetic subjects with a reversed circadian BP rhythm than in those with a normal one. Especially, cardiac autonomic dysfunction could be directly associated with a poor prognosis in diabetic subjects with a reversed circadian BP rhythm, leading to the serious cardiovascular events, including sudden deaths, observed in this study (7,17).

Although the relationship between a reversed circadian BP rhythm and an occurrence of quite divergent vascular events is not clear, the causes of fatal and serious nonfatal events, cerebro- and cardiovascular diseases and renal failure, observed in this study were similar to those in previous reports (1–10). However, most of the sudden deaths, cerebral hemorrhages, massive nasal bleeding, and vitreous hemorrhages were observed during the nighttime or early morning. The incidence of myocardial infarction has also been reported to be characterized by a sharp increase from 0600 to 0800 in nondiabetic subjects (24). Thus, the reversed circadian BP rhythm could be responsible for the occurrence of these vascular events during the nighttime or early morning. In fact, the observations of Liniger et al. (17) and of us showed that severe vascular events during a period of follow-up were more frequently counted in diabetic subjects with a nocturnal BP rise than in those with a pronounced nocturnal BP fall. Hence, nocturnal BP levels, as well as daytime BP levels, should be managed with attention to the possible role of reversed circadian rhythm in nighttime pressure-natriuresis for the improvement of prognosis in NIDDM subjects.

In conclusion, the present study clearly demonstrates that the reversed circadian BP rhythm is associated with occurrences of vascular events in NIDDM subjects. Thus, reversed circadian BP rhythm, as well as other risk factors, such as hyperlipidemia, obesity, poor glycemic control, and hypertension, should be carefully managed to prevent the development of fatal and nonfatal vascular events in diabetic subjects. In particular, further study is needed to clarify the effects of reduction in BP during the nighttime on prognoses in NIDDM subjects with a reversed circadian BP rhythm.

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