Detection of Autonomic Nervous System Abnormalities in Diabetic Patients by 24-hour Ambulatory Blood Pressure Monitoring

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Objective: To determine the relationship between 24-hr blood pressure (BP) fluctuations and autonomic nervous system dysfunction in diabetic patients using non-invasive ambulatory blood-pressure monitoring (ABPM) system.
Methods: The subjects were 39 diabetic patients free of cardiovascular diseases. 24-hr BP was monitored by a non-invasive ABPM system. The relationships among 24-hr BP fluctuations and various clinical parameters relevant to diabetes and hypertension were analyzed.
Results: Patients were divided into the diurnal hypertension (DH, n = 4), diurnal and nocturnal hypertension (DNH, n = 9), normotension (N, n = 14), and nocturnal hypertension (NH, n = 12) groups. DH and/or NH was observed in 25 (64%) patients: 13 had DH (≥ 135/85 mmHg), 21 had NH (≥ 120/70 mmHg), and 9 had both. Furthermore, 4 patients with DH but no NH (diurnal/nocturnal + / -); 9 (+ / +); 14 (- / -); and 12 (- / +). The R–R interval coefficient of variation on the EKG (CV-RR) was significantly different among the groups (N > NH > DNH > DH).
Conclusion: Autonomic nervous system dysfunction in diabetic patients had a negative influence on 24-hr fluctuations in BP. Monitoring nighttime hypertension and daily BP variation using ABPM diabetic is a potentially useful approach for identifying autonomic nervous system dysfunction and associated abnormal BP patterns that cannot be detected by routine check-ups.

Key words: ABPM, diabetes mellitus, nocturnal hypertension, CVR-R

INTRODUCTION

The long-term complications associated with diabetes mellitus include microvasculopathies (e.g., neuropathy, retinopathy, and nephropathy) and macrovasculopathies (e.g., myocardial and cerebral infarction). These complications are not related to hyperglycemia alone but also the associated comorbidities of dyslipidemia and hypertension [1–5]. Notably, the risk of cardiovascular events increases significantly in patients with hypertension [6, 7]. Accordingly, strict blood pressure (BP) control is an essential component of the overall risk management strategies of diabetes mellitus. Thus, analysis of the association between BP variability and various clinical parameters could yield important information on how to limit the progression of diabetic vasculopathies.

Diabetes mellitus is an important cause of abnormal variation in circadian BP rhythm [8]. Disrupted balance between sympathetic and parasympathetic nervous systems is believed to play a role in the pathology. In particular, damage to peripheral autonomic nervous system acts to extinguish the typical daily variation in BP [9, 10]. Moreover, abnormal variability in circadian BP can result in nocturnal hypertension, which is considered a better indicator of the severity of hypertension than diurnal hypertension [11]. Various studies have shown that the rates of cardiovascular diseases and mortality correlate with nocturnal hypertension [12, 13] and that normalization of nighttime BP level suppresses the progression of diabetic nephropathy [14]. Accordingly, monitoring daily fluctuations in BP in diabetic patients, and checking for associations with autonomic nervous system dysfunction, may help in understanding the pathophysiology and progression of such irregularities in this population.

Advances in biomedical technology, such as non-invasive ambulatory BP monitoring (ABPM), have simplified the measurement of nocturnal fluctuations in BP. Many case reports and research studies that utilize ABPM have already been reported, although the technique has been noted to have reproducibility issues [15]. However, only a few studies have so far examined autonomic nervous system dysfunction and abnormal circadian BP variation in diabetics.

The aim of the present study was to determine the relation between 24-hr BP fluctuations and autonomic nervous system function in diabetic patients. For this purpose, we recorded BP and heart rate over 24 hrs using ABPM in diabetic patients enrolled in a

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Table 1 Patient Characteristics.

Sex (M/F)	20/19
Age (years)	57.4 ± 15.1
BMI (kg/m^2)	25.1 ± 4.7
Diabetes history (years)	6.83 ± 7.32
Diabetes subtype (type 1/type 2/other)	6/31/2
Retinopathy (+/-)	7/32
HbA1c (%)	10.7 ± 2.5
R-R interval variation (CVR-R)	2.80 ± 1.28
Creatinine clearance (ml/min)	105.6 ± 38.8
UAE (mg/day)	27.0 ± 41.7
UCE (μg/day)	71.6 ± 46.6
Circadian blood pressure pattern (extreme dipper/dipper/non-dipper/riser)	1/15/19/4
Hypertension (+/-)	25/14
Hypertension group (DH/DNH/N/NH)	4/9/14/12

Data are mean ± SD or number of patients.
BMI: body mass index; UAE: 24-hrs urinary albumin excretion; UCE: urinary C-peptide excretion rate; DH: diurnal hypertension only; DNH: diurnal and nocturnal hypertension; N: normotension only; NH: nocturnal hypertension only.

hospital-based diabetes education program, and then evaluated their BP and heart rate profiles in relation to various diabetes-related parameters.

MATERIALS AND METHODS

The target population consisted of diabetes patients receiving inpatient diabetes education between 2013 and 2017. To reduce the potential of confounders in BP measurements, analysis was limited to 39 patients without any apparent history of cardiovascular disease and who were not taking anti-hypertensive medications. The clinical parameters analyzed in the present study included age, sex, body mass index (BMI: body weight/height^2 [kg/m^2]), disease duration and subtype, HbA1c level, and 24-hrs urinary C-peptide excretion rate (UCE). Patients were also assessed for diabetic microvascular damage in terms of retinopathy (+/-), nephropathy (i.e., 24-hrs urinary albumin excretion [UAE] and creatinine clearance), and neuropathy (i.e., the coefficient of variation of R-R intervals on the EKG [CVR-R]).

ABPM was carried out using a portable automatic BP monitor (TM-2431: Nihon Kohden, Tokyo), which measured BP and pulse rate every 30 minutes by the oscillometric method. The average systolic and diastolic BP during the daytime (0600-2200) and nighttime (2200-0600) were calculated. Diurnal and nocturnal hypertension were defined respectively as ≥ 135/85 and ≥ 120/70 mmHg [8]. For analytic purposes, patients were divided into four groups based on their diurnal/nocturnal hypertension status: diurnal hypertensive only (DH); diurnal and nocturnal hypertensives (DNH); normotensives; and nocturnal hypertensive only (NH). The above clinical parameters were compared among the four groups. We also examined the correlation between nocturnal/diurnal BP and CVR-R.

Patients were also classified according to the relation between daytime and nighttime BP. "Dippers" were defined as individuals with mean nocturnal BP ≥ 10 to < 20% lower than the mean diurnal BP; "extreme dippers" showed a drop of ≥ 20%. "Non-dippers" were defined as individuals with a nocturnal decline in BP of < 10%, while "risers" had higher nocturnal BP, on average, than during the daytime [16].

Results are presented as mean ± SD. Multiple-group comparisons were conducted using the Kruskal-Wallis test or one-way ANOVA; two-group comparisons were conducted using the χ^2 or Mann-Whitney U test. Spearman's rank correlation coefficient was used to examine correlations between two variables. Statistical significance was set at $p < 0.05$. Statistical processing was carried out using JMP® 13 (SAS Institute Inc., Cary, NC).

RESULTS

The study population consisted of 20 males and 19 females, aged 57.4 ± 15.1 years. BMI was relatively high (25.1 ± 4.7 kg.m^2). Thirty-one (79%) had type 2 diabetes, 6 had type 1 diabetes, and 2 had other types of diabetes. The mean duration of diabetes was 6.83 ± 7.32 years. HbA1c at admission was high (10.7 ± 2.5%) and 24-h UCE (71.6 ± 46.6 μg/d) indicated relatively well preserved endogenous insulin secretion, except for a few type 1 diabetes patients. Diabetic retinopathy was observed in 7 of the 39 (22%) patients. CVR-R was 2.80 ± 1.28%. Renal function tests showed creatinine clearance of 106 ± 39 ml/min, and 24-h UAE of 27.0 ± 41.7 mg/day (Table 1), suggesting normal albuminuria with well maintained renal function in the majority of patients.

Diurnal and/or nocturnal hypertension was observed in 25 of the 39 patients (64%): 13 had diurnal hypertension (≥ 135/85 mmHg), 21 had nocturnal hypertension (≥ 120/70 mmHg), and 9 had both. Patients were categorized based on their diurnal and nocturnal hypertension into the following groups: Those with diurnal hypertension but no nocturnal hypertension: (diurnal/nocturnal +/-, n = 4); (+/+, n = 9); (-/-, n = 14); and (-/+, n = 12, Table 1).

There were no significant differences among the four groups in terms of age, sex, BMI, disease history, type of diabetes, prevalence of retinopathy, and 24-h UAE. Furthermore, there were non-significant trends for HbA1c ($p = 0.0909$), 24-h UCE ($p = 0.0659$),

Table 2 Comparison of clinical parameters among the four hypertension groups.

	DH (n = 4)	DNH (n = 9)	N (n = 14)	NH (n = 12)	P value
Sex (M/F)	2/2	4/5	9/5	5/7	0.6679
Age (years)	67.8 ± 15.6	55.8 ± 11.8	55.4 ± 17.8	57.5 ± 14.3	0.5435
BMI (kg/m²)	24.7 ± 2.6	25.2 ± 3.5	24.0 ± 4.7	26.3 ± 6.0	0.6900
Diabetes history (years)	4.33 ± 4.04	10.4 ± 8.06	5.33 ± 4.29	6.25 ± 9.30	0.3863
Diabetes subtype (type 1/type 2/other)	1/3/0	1/8/0	3/9/2	1/11/0	0.4961
Retinopathy (+/-)	1/3	2/7	2/12	2/12	0.5988
HbA1c (%)	9.1 ± 1.0	9.5 ± 1.3	11.7 ± 3.1	11.3 ± 2.4	0.0909
R-R interval variation (CVR-R)	2.15 ± 1.01	2.16 ± 0.90	3.59 ± 1.31	2.58 ± 1.18	0.0218
Creatinine clearance (ml/min)	83.3 ± 39.8	116.8 ± 39.7	91.3 ± 36.1	123.9 ± 34.8	0.0907
UAE (mg/day)	16.1 ± 26.7	15.2 ± 18.3	31.8 ± 46.6	34.0 ± 52.5	0.6959
UCE (μg/day)	123.8 ± 29.4	76.9 ± 50.6	50.0 ± 45.7	79.0 ± 37.4	0.0659

Data are mean ± SD or number of patients.
BMI: body mass index; UAE: 24-hrs urinary albumin excretion; UCE: urinary C-peptide excretion rate; DH: diurnal hypertension only; DNH: diurnal and nocturnal hypertension; N: normotension only; NH: nocturnal hypertension only.

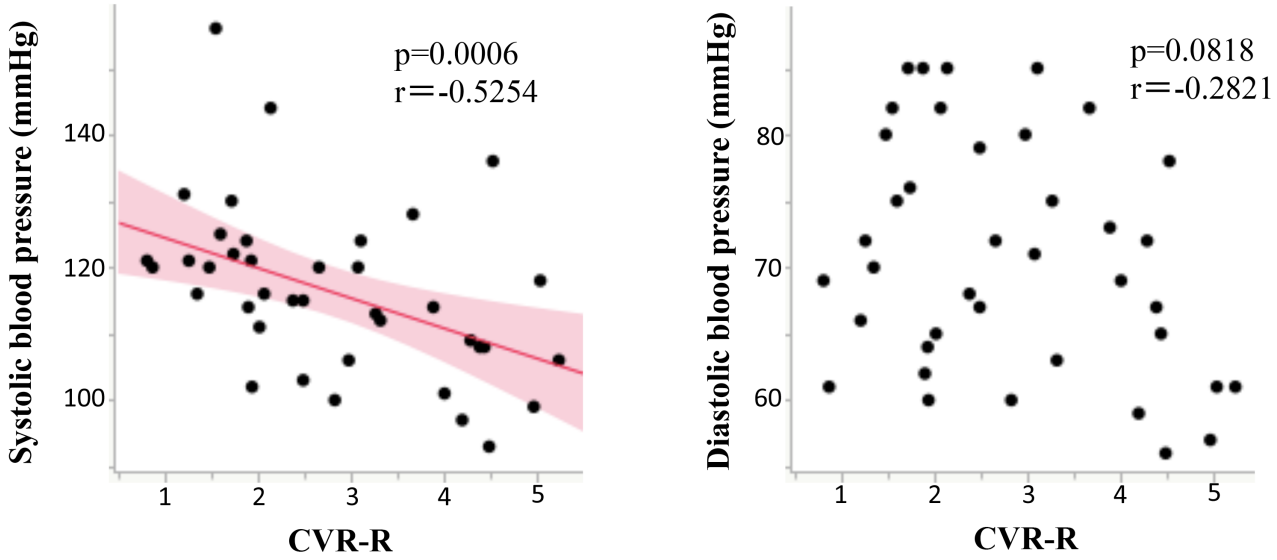

Fig. 1 Correlation between nocturnal BP and CVR-R, based on analysis by (a) systolic BP and (b) diastolic BP (n = 39, each).

and creatinine clearance (p = 0.0907). On the other hand, there were significant differences in CVR-R (p = 0.0218) among the four groups (normotensives: 3.59 ± 1.31 > NH: 2.58 ± 1.18 > DNH: 2.16 ± 0.90 > DH: 16.1 ± 26.7; Table 2, Fig. 1).

In terms of circadian BP patterns, 4 patients were classified as risers, 19 as non-dippers, 15 as dippers, and 1 as an extreme dipper. Given the small group size for risers and extreme dippers, risers and non-dippers were combined into a broadly defined "Non-Dip" group, and dippers and extreme dippers into a "Dip" group. There were no significant differences in any of the clinical parameters examined between the two groups. However, members of the NH group tended to belong to the Non-Dip group (Table 3).

Finally, we evaluated the relationship between CVR-R and systolic and diastolic BP using the ABPM data. CVR-R values correlated significantly with nocturnal/diurnal systolic BP, but not diastolic BP (Figs. 1 and 2).

DISCUSSION

Progression of diabetes is associated with the development of microvascular diseases such as neuropathy, retinopathy, and nephropathy, as well as macrovascular diseases such as myocardial and cerebral infarctions. Not only the disease is a major risk factor for arteriosclerosis; it is also associated with a high rate of hypertension. Analysis of the association between BP variability and various clinical parameters could yield important information about how to limit the progression of various diabetic complications. Based on this background, we monitored patients who had enrolled in a hospital-based diabetes education program using ABPM and evaluated their BP profiles in relation to various diabetes-related data. Our results suggest that such monitoring was useful for clarifying the specific pathologies and characteristics of individual diabetic patients.

As shown in Table 2, there was a significant differ-

Table 3 Comparison of selected clinical parameters between the Dip and Non-Dip groups.

	Dip (n = 16)	Non-Dip (n = 23)	P value
Sex (M/F)	8/8	11/12	0.8337
Age (years)	56.6 ± 17.8	58.0 ± 13.4	0.9772
BMI (kg/m^2)	24.3 ± 4.3	25.6 ± 5.0	0.4965
Diabetes history (years)	5.73 ± 6.70	7.62 ± 7.79	0.3644
Diabetes subtype (type 1/type 2/other)	3/13/0	3/18/2	0.4490
Retinopathy (+/-)	2/14	5/18	0.2501
HbA1c (%)	10.3 ± 2.5	11.2 ± 2.5	0.1984
R-R interval variation (CVR-R)	3.07 ± 1.49	2.62 ± 1.09	0.2907
Creatinine clearance (ml/min)	100.8 ± 42.2	109.3 ± 36.7	0.5602
UAE (mg/day)	29.3 ± 52.3	25.4 ± 33.5	0.7101
UCE (μg/day)	81.8 ± 49.0	63.9 ± 44.4	0.3337
Hypertension group (DH/DNH/N/NH)	4/3/8/1	0/6/6/11	0.0052

For abbreviations, see Tables 1 and 2.

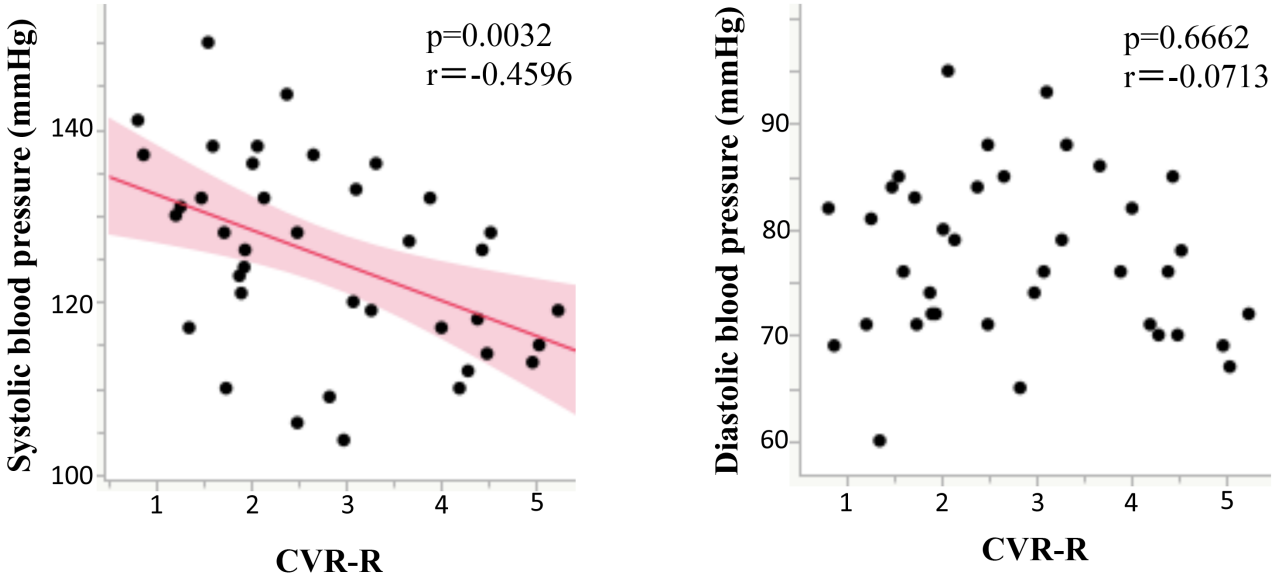

Fig. 2 Correlation between diurnal BP and CVR-R, based on analysis by (a) systolic BP and (b) diastolic BP (n = 39, each).

ence in R-R interval variability among the four groups defined by diurnal and nocturnal hypertension. This finding suggests that severe autonomic nervous system dysfunction, as represented by decreased CVR-R, may influence circadian patterns of BP variation. Specifically, a low CVR-R appears to manifest more commonly in patients with nocturnal hypertension. Accordingly, efforts to detect autonomic nervous system dysfunction as soon as possible should not be limited to performing EKGs during regular outpatient visits but to extend these to measure CVR-R. In fact, physicians should consider the diagnosis of nocturnal hypertension in patients with autonomic dysfunction. Thus, based on our data, we recommend ABPM monitoring to detect nocturnal hypertension, in addition to patient guidance, in order to determine cardiovascular event risk at an early stage. Furthermore, the results shown in Figs. 1 and 2 suggest that a low CVR-R seems to have a stronger effect on the rise in systolic BP than in diastolic BP.

Diabetic patients with autonomic nervous system dysfunction have been reported to have low CVR-R [17, 18], and that their BP rises acutely during sleep [19]. While we did not directly investigate the mechanisms of the nocturnal rise in BP, others have shown that the latter could be due to an increase in sympathetic activity and a decrease of parasympathetic activity associated with autonomic nervous system dysfunction [10]. Others considered the rise in nocturnal BP to be associated with sympathetic overactivity induced by hypoadiponectinemia, a byproduct of abnormal glucose metabolism [20] and insulin resistance [21].

Despite the lack of significant differences in the data shown in Table 2, there were borderline significant differences in 24-h UCE, creatinine clearance, and HbA1c among the four groups. C-peptide excretion is considered to be a marker of endogenous insulin secretion. The 24-h UCE was lower in normotensive patients than those of the DNH group. Patients of the N group

tended to have a shorter disease history and higher HbAc1 levels, while those of the DNH group tended to have longer disease history and lower HbAc1 levels. Based on these observations, we speculate that patients of the DNH group suffered low insulin secretion at the time of enrollment in the inpatient program, probably due to inadequate management of hyperglycemia: i.e., glucotoxicity, or strong insulin resistance [22, 23]. Admittedly, we cannot confirm this hypothesis due to insufficient information about the treatment used by the patients and the results of other hematological tests.

Creatine clearance was highest in patients of the NH group. This signifies a high prevalence of hyperfiltration (i.e., excessive glomerular filtration observed in stage 1 diabetic nephropathy) in these patients. These data corroborate with another study that showed salt-sensitive hypertension to be associated with nocturnal hypertension and hyperfiltration [24]. Normalization of BP is considered to be an essential step in inhibiting the progression of diabetic nephropathy in nocturnal hypertensives [7]. Appropriate strategies to halt the progression of renal disease should incorporate ABPM to check patients for nocturnal hypertension and, when hyperfiltration is detected at an early stage, administration of RAS inhibitors is recommended in order to reduce glomerular pressure and correct the situation. Such strategies could target renal disease more precisely and provide early treatment than current approaches.

Our results showed no significant differences in any of the clinical parameters examined in this study, between patients of the Dip and Non-Dip groups. This could be related to the reproducibility related to ABPM. In this regard, the HARVEST study [15] have shown that while ABPM achieves relatively good reproducibility for 24-h BP patterns, the same is not true for short-term variations. There is a debate on whether a given subject can be classified as a 'dipper' or 'non-dipper' since differences do exist between two observation days in about 30% of the time [25–27]. To minimize potential confounders of reproducibility, we limited our subjects to those undergoing an inpatient diabetes education program. Nonetheless, the diet provided to the patients while in hospital was likely different from that consumed at home, and consequently, weight gain and/or other factors known to influence reproducibility could still have had masked effects [11]. It was noted that a large proportion of patients of the Non-Dip group tended to have nocturnal hypertension only (although this difference was not statistically significant). This finding suggests a close relationship between non-dipping/rising BP profiles and nocturnal hypertension in diabetic patients. Further prospective studies of larger number of patients are needed with controlled weight changes and other potential confounders, in order to examine the above relation between non-dipping and nocturnal hypertensive diabetic patients.

In addition to the issues discussed above, our study has several other limitations. First, the study subjects were living in an inpatient environment as part of a diabetes education program, under conditions different from their daily lives. It is possible that this selection could have negatively affected the sleep quality of at least some individuals, which in turn may have influenced nocturnal BP. In addition, more than a few patients had begun insulin therapy or taking oral hypoglycemic agents. Thus, the short time frame of our study meant that we could not evaluate the effects of improvements in glycemic control on BP variability.

In conclusion, our study demonstrated that monitoring diabetic patients for nighttime hypertension and BP variation using ABPM is a potentially useful approach for identifying autonomic nervous system dysfunction and associated abnormal BP patterns that cannot be detected by routine check-ups. Our study analyzed only the clinical parameters of age, sex, BMI, diabetes duration and subtype, retinopathy, HbA1c, 24-h UCE, UAE, and CVR-R. Future studies should analyze a larger sample size and incorporate more variables to improve accuracy — e.g., arteriosclerotic markers, such as carotid intima-media thickness and hematological values such as cholesterol, as well as weight changes — in addition to addressing the limitations noted above.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to this article.

ETHICS APPROVAL

The research project was approved by the Institutional Review Board for Clinical Research, Tokai University Hospital (09R-071).

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