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Is there an association between non-dipping blood pressure and measures of glucose variability in type 1 diabetes?

Jaiswal Mamta, MBBS PhD[1], **Ang Lynn, MD**[2], **Mizokami-Stout Kara**[2], and **Pop-Busui Rodica, MD PhD**[2]

[1]Department of Neurology, University of Michigan, Ann Arbor, Michigan

[2]Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, Michigan

Abstract

Aim: To assess the relationship between glucose variability (GV) and non-dipping of blood pressure (BP) as a marker of cardiovascular autonomic neuropathy (CAN) among patients with type 1 diabetes (T1D).

Methods: Forty-one subjects with T1D (age 34±13 years, duration 13±6 years, HbA1c 8±1.2%) without cardiovascular disease, dyslipidemia, or hypertension at baseline were enrolled in a 3-year observational cohort study. Subjects were phenotyped for CAN with heart rate variability, cardiovascular autonomic reflex tests, and 24-h BP profiles at baseline and during follow-up. Non-dipping was defined as nocturnal systolic and diastolic BP fall of ≤ 10%. Reverse dipping BP was defined as a <0% change in the day to night for systolic and diastolic BP. Indices of GV were derived from 5-day continuous glucose monitoring obtained at 3-month intervals, and serum inflammatory biomarkers in all subjects.

Results: At baseline 10% of the T1D subjects were non-dippers. The dippers and non-dippers were similar in age, diabetes duration, glucose control, traditional cardiovascular risk factors, GV and inflammatory markers. No significant correlations were found at baseline between non-dipping nocturnal blood pressure and measures of GV. At 3 years there were no differences in risk factor profile of subjects who were non-dippers over time (progressors) and those who were dippers (non-progressors).

Conclusion: In a cohort of contemporary patients with T1D following the current standard of care in diabetes, the prevalence of non-dipping is relatively low. There were no clear phenotypes that explained the difference in the risk for non-dipping, including GV. Ambulatory blood pressure monitoring could be used as a tool for improved CVD risk stratification and development of therapeutic interventions in these patients.

Corresponding author: Rodica Pop-Busui, MD, PhD, University of Michigan, Division of Metabolism, Endocrinology and Diabetes, 5329 Brehm Tower, 1000 Wall Street, Ann Arbor, MI 48105 Phone: 734-763-7274, rpbusui@umich.edu.

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Keywords

Non-dipping blood pressure; Cardiovascular autonomic neuropathy; Glucose Variability; Type 1 diabetes

Introduction

The attenuation of the physiological nocturnal decline in the blood pressure (BP), or non-dipping, as measured by ambulatory blood pressure monitoring (ABPM) is a stronger predictor of target organ damage and CVD risk than office BP readings in subjects with type 1 (T1D) (1) and type 2 diabetes(T2D) (2,3). The prevalence of non-dipping has been reported up to 73% in patients with T1D and linked to increased risk of hypertension, retinopathy, and nephropathy (2). ABPM is currently accepted as the most sensitive method for assessing circadian BP profile and non-dipping status for estimating future CVD risk (2,3).

The etiology of non-dipping has been linked to hypertension, renal function impairment and to altered nocturnal sympathovagal balance associated with cardiovascular autonomic neuropathy (CAN) (1–4). Indeed, CAN is an independent predictor of CVD mortality and CVD events in diabetes (5). Traditionally, poor glucose control, as documented by HbA1c levels is considered the main factor driving the development of diabetic complications including CAN in patients with diabetes. Emerging evidence suggest that wide glucose fluctuations may play an important role in the development of chronic complications, including CAN, independent of HbA1c (6,7). Furthermore, chronic inflammation, mediated by increased glucose variability(GV) (8,9), is emerging as a potential critical factor in the development of diabetes complications including CAN (8). However, the effects of GV on non-dipping have not been directly studied.

The objective of this study was to evaluate the association between non-dipping, as a surrogate measure of CAN, and GV in patients with T1D and no known history of CVD. Risk factor profiles for non-dipping and inflammatory biomarkers were also evaluated as potential explanatory variables.

Subjects, Materials and Methods

Forty-one subjects with T1D were recruited from the University of Michigan Health System clinics to participate in this 3-year longitudinal observational study. Inclusion criteria: type 1 diabetes, age 18–65 years, duration ≥ 5 years, no evidence of any diabetic complications. Exclusion criteria: history of CVD, hypertension or use of antihypertensive medication (including beta blockers), chronic kidney disease, dyslipidemia, use of glucocorticoids or other medication . All study participants signed a written informed consent and the Institutional Review Board at the University of Michigan approved the study.

Study Procedures

Demographic data and anthropometric measures were collected through questionnaires and physical examination. Fasting blood samples were obtained for the measurement of glucose,

HbA1c, lipid panel, renal function tests, and inflammatory markers : interferon gamma(IFN-g), IL-1ra(interleukin), IL-1b, IL-10, monocyte chemoattractant protein (MCP-1), tumor necrosis factor alpha (TNF-a), TNF- receptor and C-reactive protein (CRP).

Assessment of GV

Continuous glucose monitoring (CGM) data were obtained at 5-minute intervals over a period of five days at baseline and every 3 months intervals for 3 years with the iPro CGM System (Medtronic, Northridge CA) (7). The following indices of GV were computed: low and high blood glucose index (LBGI and HBGI), mean amplitude of glucose excursions (MAGE), coefficient of variation (CV) of glucose, and area under the curve (AUC) for hypoglycemia and hyperglycemia (7).

Assessment of CAN

CAN was assessed by standardized cardiovascular reflex testing (CARTs) (paced deep breathing, Valsalva maneuver and postural changes) and by heart rate variability (HRV) studies performed annually for 3 years, and analyzed with the ANX 3.1 (ANSAR Inc., PA) as described (7). R-R response to paced breathing analyzed as E/I (Expiration: Inspiration) ratio, Valsalva ratio, the postural R-R response analyzed as 30:15 ratios, time-domain measures of HRV [Standard deviation of normal RR interval (SDNN) and root mean square of successive differences of normal RR intervals (RMSSD)] and frequency-domain measure of HRV [low frequency (LF) power, high frequency (HF) power and LH/HF at rest and during CARTs] (7).

Ambulatory Blood Pressure Monitoring

24-h BP profiles were obtained with a portable oscillometric recorder (Spacelabs90207, Redmond, WA), annually for 3 years to assess ABPM (1). Non-dipping of BP defined as a ≤ 10% change from day to night for systolic and diastolic BP ([mean daytime BP – mean night-time BP]/daytime BP × 100%), arithmetically equivalent to a night-to-day BP ratio of >0.9 as described (4). Reverse dipping BP was defined as a <0% change in the day to night for systolic and diastolic BP(4).

Statistical Analysis

Differences between dippers and non-dippers were evaluated using the Student’s t-test and Wilcoxon rank sum test. Spearman’s correlation coefficient (r) was calculated to evaluate the relationships between GV indices and BPV variables. In longitudinal analyses we defined as progressors: who had a worsening of non-dipping (non-dipping status remained same or change from dipper into non-dipper) and non-progressors: who had improvement in their dipping status from baseline to 3 years.

Data analysis was performed using SAS software (SAS Institute Inc., Cary, North Carolina, USA).

Results

In this cohort of patients with T1D (mean age 34 ± 13 years, duration 13 ± 6 years, 61% females, HbA1c 8 ± 1.2%) the prevalence of BP non-dipping at baseline was 10%. Reverse-

dipping, defined as nocturnal BP fall of < 0% was found in only 2 subjects. None of the subjects had evidence of orthostatic hypotension (defined as a drop of 20 mm Hg of systolic BP and 10 mmHg of diastolic BP from supine to standing position)(1). Table 1 shows the clinical characteristic of the subjects with T1D stratified by their non-dipping status. At baseline there were no differences in clinical characteristics between these groups. Measures of glucose control (HbA1c 7.2±1.4% vs. 8.0±1.2%, P=0.32), GV and inflammatory biomarkers were also similar between the groups. There were no significant differences between the levels of inflammatory biomarkers between dippers and non-dippers (Table 1).

No significant correlations were found at baseline between BPV (% dipping of BP over 24 hour) and measures of GV [HBGI (r=−0.05, P=0.71), LBGI (r=0.05, P=0.75),CV (r=0.02,P=0.45), AUC Hypo (r=0.055,P=0.73), AUC Hyper (r=0.045,P=0.62), and MAGE(r=0.39, P=0.062)] and HbA1c(r= 0.09,P = 0.53).

During follow-up, 24 (58%) out of the 41 subjects, remained non-dippers or changed from dippers to non-dippers (progressors). We evaluated the potential risk factors that could explain a progressive phenotype in BP dipping status. Neither the overall glucose control(HbA1c), nor measures of GV over time were different between these 2 groups. In addition, there were no differences in any other traditional risk factors assessed, including BP, lipid profiles or weight, explaining the risk for non-dipping (Table 2).

Discussion

In this cohort of relatively healthy adults with T1D, with mean diabetes duration of 14 years we found a low prevalence (10%) of non-dipping status at baseline. However, after 3 year of follow-up, with the current standard of care we found that 58% of the subjects had a progressive phenotype. Interestingly, there were no associations between non-dipping BP and measures of CAN at baseline. In addition, there were no differences in any measures of GV, metabolic parameters or inflammatory markers between dippers and non-dippers. We then examined the subjects based on their progression/improvement of dipping status overtime (progressors vs non-progressors). We did not find significant differences in glucose control, metabolic profiles, and measures of GV and CAN parameters in these 2 groups although there was a trend towards increased inflammatory biomarkers in non-dippers.

Our results are in contrast with earlier studies in T1D (9,10) that reported prevalence rates for non-dipping of 51%, and with more recent data reported by Pistrosch et al who found a prevalence of 73% for non-dipping in a cohort of 107 subjects with type 2 diabetes and hypertension (11). However, their study population was older with higher HbA1c , longer duration of diabetes, higher LDL-c, and >50% subjects had several diabetic complications (11). The authors also evaluated cross-sectional associations between BP circadian variation and blood glucose levels measured before and 2 hours after meals, and reported that non-dippers exhibited higher postprandial glucose excursions than dippers, whereas the levels of fasting glucose and HbA1c were comparable between the two groups (11). Stella et al reported that nocturnal non-dipping occurred in approximately 28% of their T1D cohort (2). These findings may add additional prognostic values as both postprandial glucose excursions and non-dipping are reported risk factors for CVD events (2, 3, 8). There have also been

reports of association between increased nocturnal BP and progression to microalbuminuria and nephropathy with increased mortality in patients with diabetes (12). Thus GV acts as a potential risk factor driving the non-dipping BP which may progressively lead to silent and clinically covert CVD.

Several reports using power spectral analysis of HRV suggest that a reduction in parasympathetic nervous system activity may contribute to the non-dipping BP pattern (1). However, we did not find any significant correlations between measures of HRV, or CARTs and BPV. Stella et al reported no association between non-dipping status and CAN and nephropathy in their T1D cohort(2). In contrast with our findings, Spallone et al reported that non-dipping is highly sensitive and specific in discriminating between patients with T1D with and without CAN (13). However, the authors used an alternative definition of non-dipping (day-night change in BP ≤ 0%), when in general non-dipping is defined as ≤10% drop in nocturnal BP (2) as we used. It is thus possible that the differences in outcome measures may explain the discrepancy in our findings. Therefore, using uniformly standardized definitions and cut-offs for non-dipping is needed to better identify the true relationship between non-dipping and CAN.

Some studies have found association between CAN and inflammatory biomarkers such as interleukin-6 but not TNF-α in newly diagnosed T2D subjects (14). We did find increased levels of all inflammatory biomarkers and a marginally significant increase level of TNF-a levels in the progressors.

The strengths of our study are the comprehensive characterization of autonomic dysfunction, BPV and GV using state-of-the-art, well-validated, sensitive and specific measures, as well as the consistent evaluations during follow-up. Study limitations include the small sample size, a relatively healthy cohort, and relatively shorter follow-up period which could have impacted our ability to find any significant associations between GV and non-dipping pattern. Although the aim of our study was to evaluate non-dipping status in subjects with type 1 diabetes, given that only 2 subjects had reverse-dipping, we could not examine the relationship between reverse dipping and CAN in this cohort.

In summary, in a cohort of contemporary patients with T1D following the current standard of care in diabetes, the prevalence of non-dipping was relatively low. Among the factors evaluated, there were no clear phenotypes that explained the difference in the risk for non-dipping, including GV. However, since the non-dipping pattern is associated with confirmed increased CVD risk and mortality in diabetes (10), ABPM could be used as a tool for improved CVD risk stratification and development of therapeutic interventions in these patients.

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Table 1.

Baseline characteristics in subject with type 1 diabetes by their dipping status

Variable	Non-dippers N 4 (10%)	Dippers N 37 (90%)	P-value
Age, years	43 ± 14	34 ± 13	0.32
Duration, years	16 ± 11	13 ± 6	0.70
BMI, kg/m^2	27 ± 4	26 ± 5	0.77
Systolic BP , mm Hg	118 ± 4	117 ± 12	0.75
Diastolic BP, mm Hg	68 ± 11	73 ± 7	0.38
Mean Daytime Systolic BP , mm Hg	123 ± 10	125 ± 10	0.68
Mean Daytime Diastolic BP , mm Hg	73 ± 9	76 ± 6	0.18
Mean Nighttime Systolic BP , mm Hg	120 ± 9	113 ± 10	0.04
Mean Nighttime Diastolic BP, mm Hg	68 ± 11	73 ± 7	0.38
HbA1c, %	7.2 ± 1.4	8.0 ± 1.2	0.32
HbA1c, mmol/mol	54 ± 22	64 ± 21	0.32
LDL-c, mg/dl	89 ± 17	92 ± 22	0.81
HDL-c, mg/dl	60 ± 14	64 ± 20	0.58
Triglycerides, md/dl	51 ± 18	69 ± 25	0.14
Serum Creatinine, mg/dl	1.0 ± 0.3	0.8 ± 0.2	0.33
HBGI	9.8±10.5	9.9±6.7	0.97
LBGI	3.1 ± 2.6	2.7 ± 2.6	0.82
AUC Hyperglycemia	41589 ± 34745	33208 ± 36634	0.64
AUC Hypoglycemia	2660 ± 2861	2867 ± 2521	0.54
MAGE	99.3 ± 51.2	136.7 ± 29.8	0.33
CV glucose	0.42 ± 0.9	0.48 ± 0.29	0.45
IFN-g, pg/mL	2.6 (1.6,4.7)	4.3(1.9,12.9)	0.32
IL-10, pg/mL	20.6 (10.6,23.1)	2.85(1.73.8)	0.21
IL-17A, pg/mL	1.7 (1.5,3.3)	3.75(1.6,7.7)	0.37
MCP-1, pg/mL	595 (336,889)	568(429,746)	0.98
TNF-a, pg/mL	7.05(5.8,8.1)	7.7(6.2,9.6)	0.47
CRP, ng/mL	0.15(0.1,0.4)	1.2(0.1,4.3)	0.13
E:I ratio	1.21(0.11)	1.23(0.12)	0.21
Valsalva ratio	1.31(0.14)	1.28(0.17)	0.24
30:15 Ratio	1.17 ± 0.08	1.27 ± 0.18	0.05
Resting LF, ms	3.7 ± 3.9	2.7 ± 2.4	0.29
Resting HF, ms	3.1 ± 3.3	2.8 ± 3.7	0.80
Resting LF:HF Ratio	1.5 ± 0.6	2.4 ± 2.2	0.15
Deep Breathing LF, ms	0.94 ± 0.82	0.85 ± 0.58	0.65
Deep Breathing HF, ms	18.2 ± 16.8	27.1 ± 24.7	0.22
Deep Breathing LF:HF Ratio	3.6 ± 8.9	3.2 ± 7.8	0.10

Variable	Non-dippers N 4 (10%)	Dippers N 37 (90%)	P-value
SDNN , ms	52.5 ± 21.9	52.2 ± 21.5	0.96
RMSSD, ms	45.2 ± 33.0	36.7 ± 25.1	0.34

Data are presented as mean±SD or median(IQR). BMI: body mass index, BP: blood pressure, LDL low density lipoprotein, HDL: high density lipoprotein, HBGI: high blood glucose index, LBGI: low blood glucose index, AUC: area under the curve, MAGE: mean amplitude of glycemic index , CV: coefficient of variabtion,IFN-g: interferon gamma, IL: interleukin, MCP: Monocyte chemoattractant protein-1, TNF-a: tumor necrosis factor alpha, R: receptor, CRP: c reactive protein, E:I : expiration inspiration, LF: low frequency power, HF: high frequency power, SDNN: standard deviation of normal RR interval, RMSSD: root mean square of the difference of the successive normal RR interval.

Table 2.

Differences in the characteristics of subjects with type 1 diabetes who progressed vs those who did not progress over 3 years

Variable	Progressors = 24	Non-progressors = 17	P value
Age , years	37 ±14	33±12	0.30
Duration, years	13±6	14±7	0.51
BMI, kg/m^2	25±5	28±4	0.03
Systolic BP, mm Hg	117±13	117±10	0.98
Diastolic BP, mm Hg	73±7	72±9	0.79
Mean Daytime Systolic BP, mm Hg	125 ± 9	128± 10	0.71
Mean Daytime Diastolic BP, mm Hg	75 ± 9	78 ± 6	0.21
Mean Nighttime Systolic BP, mm Hg	123 ± 9	112 ± 10	0.25
Mean Nighttime Diastolic BP, mm Hg	65± 11	71 ± 7	0.22
HbA1c,%	8±1.3	7.8±1.2	0.64
HbA1c, mmol/mol	64±22	58±21	0.64
Cholesterol , mg/dl	174±31	161±25	0.13
LDL-c, mg/dl	95±25	88±17	0.42
HDL-c, mg/dl	66±23	61±16	0.46
Triglycerides, mg/dl	73±28	60±20	0.13
Serum Creatinine, mg/dl	0.9±0.2	0.8±0.2	0.63
AUC Hypo	2907±3362	2420±2336	0.79
AUC Hyper	2874±4362	2790±4336	0.65
HBGI	9.3±6	10.8±8.3	0.77
LBGI	3±2.9	2.6±2.3	0.74
MAGE	125±35.1	139.6±33.6	0.67
IFN-g,pg/mL	12.6±26.6	7.5±8.3	0.84
IL-10, pg/mL	15.2±26.2	13.8±24.9	0.92
IL-17A, pg/mL	6.1±6.2	4.1±5.2	0.12
MCP-1, pg/mL	647±245	548±248	0.25
TNF-a, pg/mL	8.7±2.9	7±2.1	0.05
CRP, ng/mL	3±4.7	1.7±2.1	0.28

Data are presented as mean ± SD. BMI: body mass index, BP: blood pressure, LDL low density lipoprotein, HDL: high density lipoprotein, DySF: dynamic stress factor, HBGI: high blood glucose index, LBGI: low blood glucose index, MAGE: mean amplitude of glycemic index , AUC: area under the curve,IFN-g: interferon gamma, IL: interleukin, MCP: Monocyte chemoattractant protein-1, TNF-a: tumor necrosis factor alpha, R: receptor, CRP: c reactive protein