Nighttime blood pressure, nighttime glucose values, and target-organ damages in treated type 2 diabetes patients

Yuichiro Yano [a,*,1], Manabu Hayakawa [b,c,1], Kazuo Kuroki [c], Hiroaki Ueno [d], Sho-ichi Yamagishi [e], Masayoshi Takeuchi [f], Takuma Eto [g], Naoto Nagata [b], Masamitsu Nakazato [d], Kazuyuki Shimada [a], Kazuomi Kario [a]

[a] Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan
[b] Division of Community and Family Medicine, University of Miyazaki, Miyazaki, Japan
[c] Internal Medicine, Kushima City Hospital, Miyazaki, Japan
[d] Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan
[e] Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Fukuoka, Japan
[f] Department of Advanced Medicine, Medical Research Institute, Kanazawa Medical University, Kanazawa, Japan
[g] Eto Cardiology and Internal Medicine, Miyazaki, Japan

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ABSTRACT

Objective: The associations between nighttime blood pressure (BP) and cardiovascular risk are well established. However, the associations between nighttime glucose values, including nocturnal hypoglycemia, and cardiovascular risk in diabetes remain unclear.
Methods: In this cross-sectional study of 49 treated type 2 diabetes patients (mean, 67.3 years; 61.0% men; mean treatment duration, 9.4 years), we performed 24-h continuous glucose monitoring simultaneously with BP monitoring, and evaluated several target-organ damages (echocardiographic left ventricular mass index [LVMI], urinary albumin excretion [UAE], carotid-artery intima-media thickness [IMT], and brachial-ankle pulse wave velocity [baPWV]).
Results: Nighttime average systolic BP values were independently associated with the extent of LVMI, log-transformed UAE, or baPWV (all $P < 0.05$). In contrast, nighttime average glucose values, rather than daytime glucose values or glucose variability, were independently associated with the extent of common carotid-artery IMT (CCA-IMT) or baPWV (all $P < 0.05$). We divided the study participants into 3 groups according to the nighttime glucose values (a group with nighttime average glucose values <161 mg/dl [reference], a group with nocturnal hypoglycemia [<70 mg/dl at least one point during sleep], and a group with nighttime average glucose values ≥161 mg/dl), and compared the extent of target-organ damages among them. Patients with nighttime average glucose values ≥161 mg/dl, but not those with nocturnal hypoglycemia, had the highest values of CCA-IMT or baPWV among the 3 groups, and the differences remained significant even after adjustment for covariates (both trend $P < 0.05$ by ANCOVA).
Conclusions: Among treated type 2 diabetes, high nighttime BP and/or glucose values were associated with a high degree of cardiovascular remodeling.

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1. Introduction

Due to advances in medical technology, blood pressure (BP) or glucose values can be evaluated clinically not only during waking, but also sleeping time periods. In the field of BP management, the superiority of nighttime BP levels as captured by ambulatory BP monitoring, rather than daytime BP or office BP values, for predicting target-organ damages or the development of cardiovascular disease has been reported in hypertensive patients [1–3].

In contrast, among diabetes subjects, evidence to demonstrate associations between nighttime glucose values as captured by continuous glucose monitoring (CGM), including the presence or absence of nocturnal hypoglycemia, and target-organ damages is lacking. Moreover, there is no information as to whether nighttime blood glucose values are more or less associated with target-organ

* Corresponding author. Tel.: +81 285 58 7344; fax: +81 285 44 5317.
 E-mail address: yyano@jichi.jp (Y. Yano).
[1] Contributed equally to this study.

damages than are daytime glucose, glucose variability, or post-prandial glucose values during anti-hyperglycemic treatments.

In the present study, therefore, we performed 24-h BP monitoring and 24-h CGM simultaneously among treated type 2 diabetes patients, and comprehensively examined whether or not nighttime BP and/or nighttime glucose values would be associated with the extent of target-organ damages (i.e., cardiac hypertrophy, urinary albumin excretion [UAE], carotid-artery intima-media thickness [IMT], and brachial-ankle pulse wave velocity [baPWV]) independently of other cardiovascular factors, including other parameters of 24-h BP monitoring or CGM data.

2. Methods

From April 2010 to February 2012, we prospectively recruited 54 consecutive ambulatory patients with treated type 2 diabetes mellitus who were ≥20 years old and who were hospitalized at Kushima City Hospital (Miyazaki, Japan) because of their poor glycemic control (i.e., Hemoglobin A1c [HbAlc] ≥6.5%). This study was approved by the institutional review board at Miyazaki University as well as a local institute (Kushima City Hospital), and written informed consent was obtained from all participants. The exclusion criteria for this study were as follows: a recent history (within 6 months) of cardiovascular diseases, such as coronary artery disease, cerebrovascular disease, and heart failure; presence of inflammatory diseases (e.g., acute infection, autoimmune diseases); presence of malignant diseases; presence of chronic atrial fibrillation; and changes in the use of any anti-hypertensive drugs, anti-hyperglycemic drugs, or statins for the last 3 months. All patients completed a health questionnaire and provided their complete medical history (smoking status, use of medications, and past medical history). Patients then underwent blood and urine sampling, 24-h BP monitoring, and 24-h CGM while limiting their physical activity. To ensure equivalent food calorie intake as well as food intake time among study participants, their meals were comprised as follows: (i) calorie intake of 30 kcal/kg/day divided equally into breakfast, lunch, and dinner servings; (ii) content of 50% carbohydrates, 30% fat, and 20% protein; (iii) breakfast at 7:00–7:30, lunch at 12:00–12:30, and dinner at 19:00–19:30.

2.1. Twenty four-hour BP monitoring, CGM, and blood and urine examinations

At least 1 day after the admission, all patients were equipped with a 24-h CGM (Medtronic MiniMed, Northridge, CA) simultaneously with a 24-h BP monitoring (TM-2425; A&D Co. Inc., Tokyo, Japan). On the morning of the next day (6:00–7:00 AM), the spot urine and fasting blood samples were collected and sent to a commercial laboratory (SRL Inc., Tokyo, Japan); all assays were performed within 24-h at this single laboratory center. Patients used their prescribed anti-hyperglycemic or anti-hypertensive drugs as usual during the examination.

CGM measures the subcutaneous interstitial glucose concentration, which closely approximates blood glucose after a short-time lag [4–6], every 5 min for up to 24-h using a glucose oxidative-based method. During CGM, appropriately trained nurses checked the blood glucose levels of the patients with a self-monitoring blood glucose device 4 times per day. Then, they entered the self-monitoring blood glucose data into the CGM device to calibrate the CGM values. After 24-h of monitoring, the recorded data were downloaded into a personal computer for analysis of the glucose profile, including the average and standard deviation of glucose values. Twenty four-hour BP monitoring was also performed with an automatic oscillometric method device at 30-min intervals [7]. For all patients, more than 80% of waking and more than 80% of sleeping BP readings were valid.

Subjects recorded their waking time and bedtime, and we define daytime and nighttime BP or glucose values as the average of values from each of these two periods. Nocturnal systolic BP dipping was calculated as (daytime systolic BP − nighttime systolic BP) × 100/daytime systolic BP. The standard deviation of glucose values was assessed as a marker of glucose variability [8]. To examine the associations of post-prandial glucose values or post-prandial glucose change from the pre-prandial state (i.e., post-prandial glucose spike) with the extent of target-organ damages, average glucose values obtained by CGM at 30-min before each meal or at 120-min after each meal were calculated. According to the American Diabetes Association guidelines, nocturnal hypoglycemia was defined as a glucose value below 70 mg/dl at one or more points during nighttime [9].

In some patients ($n = 43$), the 3% oxygen desaturation index was also recorded by a pulse oximeter during the nighttime when 24-h BP monitoring and CGM were performed. This information is described in detail in the Supplementary Data.

The value for HbA1c was estimated as a National Glyco-hemoglobin Standardization Program equivalent value calculated with the following formula [10]: HbAlc (%) = HbAlc (Japan Diabetes Society) (%) + 0.4%. To estimate renal function, the estimated glomerular filtration rate (eGFR) derived using the following equation was used [11]: eGFR (mL/min/1.73 m^2) = 194 × age (years)$^{-0.287}$ × serum creatinine (mg/dl)$^{-1.094}$ (if women × 0.739).

2.2. Assessment of target-organ damages

As described in detail in the Supplementary Data, a trained physician (Y.Y.) unaware of the patient's laboratory and CGM or 24-h BP monitoring data performed the carotid and cardiac ultrasonography on all participants. Left ventricular mass index (LVMI) was calculated using the Devereux formula indexed to body surface area [12]. None of the patients had an impaired (<45%) ejection fraction on echocardiography in the present study. The carotid arteries were examined bilaterally at the level of the common-carotid artery (CCA), the bulb, and the internal-carotid artery (ICA), as measured from both transverse and longitudinal orientations. The region with the thickest IMT was measured and was included in our analysis, and the value was calculated as the mean of the single thickest point in the far wall on both sides of the structure. The repeatability analysis of LVMI or carotid-artery IMT is shown in the Supplementary Data [13]. The UAE in the morning spot urine was assessed by a turbidimetric immunoassay (SRL Inc., Tokyo, Japan), and expressed as the urinary albumin/creatinine ratio (mg/g·Cr). The intraassay and interassay coefficients of all tests were <4%, respectively. Finally, we measured baPWV as an index of large arterial stiffness [14,15]. The precise methods of baPWV measurement were described in the Supplementary Data. In brief, baPWV was measured using a volume-plethysmographic device (form PWV/ABI; Omron Colin Co., Ltd., Tokyo, Japan) with four cuffs matched with oscillometric sensors, which were wrapped around the upper arms and ankles, and then the pulse volume records of the bilateral brachial and tibial arteries were monitored during a continuous deflation of the cuffs. The measurements were made in the supine position for at least 5 min, and the mean of the right baPWV and left baPWV was used for the statistical analyses.

2.3. Statistical analysis

All statistical analyses were performed with SPSS version 18.0 J software (SPSS, Chicago, IL). Variables with normal distribution were expressed as the means ± standard deviation, whereas variables