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Influence of HbA1c on short-term blood pressure variability in type 2 diabetic patients with diabetic nephropathy*

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Abstract: The aim of this study was to understand the characteristics of blood pressure (BP) variability in subjects with diabetic nephropathy (DN), and identify the probable predictors affecting BP variability. Fifty-one chronic kidney disease (CKD)-hypertensive patients without diabetes (NDN group) and sixty type 2 diabetic patients with overt DN (DN group) were enrolled in this study. The values of short-term BP variability were obtained from 24 h ambulatory BP monitoring (ABPM). Variance analysis or nonparametric analysis revealed that 24-h systolic BP variability and nighttime systolic BP variability of the DN group were significantly higher than those of the NDN group [(12.23±3.66) vs. (10.74±3.83) mmHg, $P<0.05$; (11.23±4.82) vs. (9.48±3.69) mmHg, $P<0.05$]. Then the patients of the DN group were divided into two groups according to glycated hemoglobin (HbA1c) level: Group A (HbA1c<7%) and Group B (HbA1c≥7%), and the *t*-test showed that patients in Group B had larger 24-h diastolic, daytime diastolic, and nighttime systolic/diastolic BP variability compared with Group A. In the DN group, partial correlation analysis revealed that HbA1c exhibited a strong association with 24-h diastolic, daytime diastolic, nighttime systolic and diastolic BP variability ($P<0.001$, $P<0.001$, $P<0.05$, and $P<0.001$, respectively). Taken together, larger short-term BP variability was detected in hypertensive type 2 diabetic patients with overt nephropathy and renal insufficiency. It may imply that the optimal BP variability level could benefit from a better glycaemic control.

Key words: Short-term blood pressure variability, Diabetic nephropathy, Glycated hemoglobin (HbA1c), Hypertension, Glycaemic control

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1 Introduction

Hypertension is one of the most common co-morbidity symptoms in patients with diabetes, and it exists in up to 80% of diabetic patients with overt nephropathy. A significant number of patients have hypertension or rising blood pressure (BP) even in the earlier stages of diabetic nephropathy (DN) and it contributes to subsequent cardiovascular morbidity and mortality. Cardiovascular disease (CVD) is the main cause of death in patients with chronic kidney disease (CKD), in particular, DN (Adler *et al.*, 2003), and hypertension is a major risk factor for CVD in CKD (Adler *et al.*, 2000). However, it has been clarified that office BP or clinic BP measurements were the least predictive indicator of CVD either in diabetic or non-diabetic patients (Kamoi *et al.*, 2002), and BP variability has been recently considered as consistently predicting the risk of future cardiovascular events independent of mean BP (Kikuya *et al.*, 2000; Verdecchia *et al.*, 2007). Eguchi *et al.* (2009) observed that neither an abnormal dipping pattern of the circadian rhythm of BP nor the morning BP surge was a predictor of CVD events, whereas the nighttime BP variability appeared to be a strong predictor, independent of ambulatory blood pressure level and other traditional risk factors in type 2 diabetic mellitus.

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Previous studies have shown that BP variability is a complex phenomenon that includes both short-term and long-term changes (Mancia and Parati, 2000). This phenomenon of BP fluctuation has been shown to depend on sympathetic vascular modulation and changes in arterial distensibility (Parati *et al.*, 1996; Pickering, 1998). Increasing evidence has shown that sympathetic overactivity, impaired baroreflex sensitivity, and arterial stiffness in diabetes may give rise to higher BP fluctuation, severe target organ damage (Parati *et al.*, 1987; Mancia *et al.*, 2001), and the subsequent higher frequency of CVD events (Kikuya *et al.*, 2000).

However, studies on BP variability in DN patients are lacking and factors that affect BP variability in DN patients are also seldom studied and clearly elucidated. More evidence on BP variability is needed to lead to a more precise controlling of CVD in DN patients. In this study, data from the recordings of 24-h ambulatory BP monitoring (ABPM) performed in hospitalized DN and NDN patients were obtained to clarify the characteristics of BP variability and analyze the factors that might influence short-term BP variability in patients with DN.

2 Subjects and methods

2.1 Subjects

Sixty Chinese hospitalized hypertensive patients (38 men and 22 women aged (59±13) years) with type 2 diabetes mellitus with overt nephropathy (DN group) and fifty-one hypertensive patients (30 men and 21 women aged (53±16) years) with non-diabetic CKD, whom were diagnosed with primary glomerulonephritis (NDN group), were enrolled in our study. Inclusion criteria were an age ≥18 years, mild-to-moderate hypertension (clinic systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg or receiving antihypertensive agents), and estimated glomerular filtration rate (eGFR) ≥15 ml/(min·1.73 m²). Renal function was assessed with eGFR using the abbreviated MDRD (modification of diet in renal disease study) equation. Exclusion criteria included patients who were receiving dialysis or renal transplantation, and patients with clinically significant heart disease, stroke, renal artery stenosis, hepatic dysfunction, pheochromocytoma, hyperthyroidism, and hyperaldosteronism. For hypertensive patients on admission, BP was treated and optimized according to the guidelines with antihypertensive drugs [calcium channel blockers (CCBs), α-blockers, β-blockers, and angiotensin II type 1 receptor blockers (ARBs)] to try to attain normotensive BP values. Additionally, the use of antihypertensive agents and erythropoietin was recorded. The main demographic and clinical characteristics of the population enrolled in this study are detailed in Table 1. The study was approved by the ethics committee of West China Hospital of Sichuan University. According to the level of glycated hemoglobin (HbA1c), the DN group was divided in two subgroups: Group A (HbA1c<7%) and Group B (HbA1c≥7%).

2.2 ABPM and short-term BP variability

ABPM was performed every 30 min with a fully automatic device (Spacelab-90217, USA). BP was measured using a cuff with the oscillometric method. Short-term BP variability (24-h BP variability, daytime and nighttime BP variability) was defined as the within-subject SD of all systolic and diastolic readings at 30-min intervals during the daytime and nighttime measurement periods, respectively. The patients were instructed to fill out individual diaries to record the time of sleeping, rising and other daytime activities. Therefore, the terms of 'daytime' and 'nighttime' used in this study reflected the average period during which the patients were awake/upright and asleep/supine, respectively. In each individual, the daytime and nighttime values were determined based on the individual diaries. The patients with a >20% incidence of missing values or missing values for more than two consecutive hours had received repeated ABPM. The following readings were omitted because of technical artifacts: systolic BP >240 or <70 mmHg, diastolic BP >150 or <40 mmHg, and pulse pressure >150 or <20 mmHg compared with the immediately preceding or successive values. Circadian rhythm of BP was calculated by the following equation: circadian rhythm of BP=(daytime average systolic BP−nighttime average systolic BP)/(daytime average systolic BP)×100%. Circadian rhythm of BP with nocturnal BP decline of 10%–20% was considered a normal dipping pattern, while circadian rhythm of BP with nocturnal BP decline of <10% was considered an abnormal non-dipper pattern.

Table 1 Clinical data of the patients in the DN group and the NDN group

Parameter	DN group	NDN group	*P*
Number of patients	60	51	
Age (year)	58.68±12.75	53.10±16.44	NS
Sex (male/female)	38/22	30/21	NS
Current smoker	22 (36.7%)	16 (31.4%)	NS
Duration of diabetes (month)	114.00 (117.00)		
No. of antihypersensitive drugs	1.92±1.01	2.29±0.92	NS
CCB	37 (62%)	40 (78%)	NS
ACEI & ARB	27 (45%)	14 (27%)	NS
α-Blocker	17 (28%)	19 (37%)	NS
β-Blocker	21 (35%)	21 (41%)	NS
Diuretics	7 (12%)	2 (4%)	NS
BMI (kg/m²)	24.97 (3.81)	23.44 (3.23)	NS
HGB (g/L)	102.83±29.00	107.02±27.84	NS
HCT (L/L)	0.32±0.09	0.33±0.08	NS
CRP (mg/L)	4.22 (26.63)	4.50 (9.06)	NS
Fasting blood glucose (mmol/L)	5.98 (2.85)	5.01 (0.65)	<0.001
HbA1c (%)	6.60 (1.75)	5.55 (1.45)	0.001
Serum urea nitrogen (mmol/L)	12.24 (6.91)	12.98 (10.23)	NS
Serum creatinine (μmol/L)	198.00 (189.55)	237.30 (241.10)	NS
eGFR (ml/(min·1.73 m²))	31.96 (38.83)	22.53 (30.96)	NS
24-h urinary protein excretion (g)	2.85 (6.04)	1.43 (2.94)	NS
Serum total cholesterol (mmol/L)	4.48 (2.15)	4.47 (1.96)	NS
Serum triglycerides (mmol/L)	1.55 (1.38)	1.55 (1.14)	NS
LDL (mmol/L)	2.47 (1.56)	2.34 (1.15)	NS
HDL (mmol/L)	1.23 (0.51)	1.12 (0.66)	NS
Ca (mmol/L)	2.10 (0.21)	2.09 (0.13)	NS
P (mmol/L)	1.22 (0.28)	1.23 (0.54)	NS
24hSBP (mmHg)	142.67±16.18	139.12±18.90	NS
24hSBPV (mmHg)	12.23 (3.66)	10.74 (3.83)	0.025
24hDBPV (mmHg)	8.02±1.93	8.30±2.40	NS
dSBPV (mmHg)	11.55 (3.52)	11.07 (5.26)	NS
dDBPV (mmHg)	7.72±1.90	8.13±2.40	NS
nSBPV (mmHg)	11.23±4.82	9.48±3.69	0.038
nDBPV (mmHg)	7.79±3.55	7.46±3.09	NS
Number of patients with non-dipper circadian rhythm of BP	56 (93.33%)	48 (94.11%)	NS

Data are expressed as mean±SE, number (percentage), or median (interquartile). Variance analysis or nonparametric-analysis was used. DN: diabetic nephropathy; CCB: calcium channel blocker; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II type 1 receptor blocker; BMI: body mass index; HGB: hemoglobin; HCT: hematocrit; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; HDL: high density lipoprotein; 24hSBP: 24-h systolic BP; 24hSBPV: 24-h systolic BP variability; 24hDBPV: 24-h diastolic BP variability; dSBPV: daytime systolic BP variability; dDBPV: daytime diastolic BP variability; nSBPV: nighttime systolic BP variability; nDBPV: nighttime diastolic BP variability; BP: blood pressure; NS: not significant

2.3 Laboratory measurements

Blood and urine samples were collected after an overnight fast. Levels of HbA1c, hematocrit, urea nitrogen, creatinine, total cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), fasting blood glucose and 24-h urinary protein excretion were measured by routine methods in West China Hospital of Sichuan University. HbA1c methods were calibrated by the high performance liquid chromatography (HPLC) method until September, 2010.

2.4 Statistical analysis

All values are given as the mean±standard error (SE). Chi-square test and variance analysis were used to test differences between the DN and NDN groups. According to the HbA1c level, the DN group was divided into Group A (HbA1c<7%) and Group B (HbA1c≥7%), and a *t*-test was used for comparison between Groups A and B. Partial correlation analysis was performed to find the factors that correlated with short-term BP variability. Non-parametric analysis was used when the data were not suitable for the *t*-test or variance analysis. IBM SPSS 20.0 statistical software was used and a calculated difference of $P<0.05$ was considered statistically significant.

3 Results

3.1 Clinical data on patients' BP variability between the DN and NDN groups

Variance analysis or nonparametric analysis was used to test the differences between the DN and NDN groups. The results showed that no significant difference was found in age, sex, body mass index (BMI), urea nitrogen, creatinine, eGFR, total cholesterol, triglycerides, LDL, HDL, hematocrit, 24-h urinary protein excretion, or antihypertensive agents (Table 1). The subcutaneous injection of erythropoietin was also prescribed for the treatment of renal anemia. Compared with the NDN group, patients in the DN group had significantly higher levels of fasting blood glucose and HbA1c (Table 1). Additionally, 24-h systolic BP variability and nighttime systolic BP variability were significantly higher in patients with DN. The circadian rhythms of BP of most patients in both DN and NDN groups exhibited a non-dipping

profile and the proportion of patients with a non-dipping profile of circadian rhythm of BP in the DN and NDN groups showed no significant difference. Analysis of variance (ANOVA) revealed this.

Table 2 Comparison of DN patients with different levels of HbA1c

Parameter	Group A (HbA1c<7%)	Group B (HbA1c≥7%)	*P*
Number of patients	28	20	
Age (year)	56.93±11.47	61.85±14.17	NS
Sex (male/female)	19/9	10/10	NS
Duration of diabetes (month)	72.00 (93.00)	130.00±81.53	NS
BMI (kg/m²)	26.04±4.16	24.22 (3.65)	NS
CCB	15 (54%)	16 (80%)	NS
ACEI & ARB	15 (54%)	7 (35%)	NS
α-Blocker	8 (29%)	6 (30%)	NS
β-Blocker	7 (25%)	7 (35%)	NS
Diuretics	4 (14%)	1 (5%)	NS
Fasting blood glucose (mmol/L)	6.14 (3.76)	7.40 (4.13)	NS
Serum urea nitrogen (mmol/L)	11.48 (4.61)	11.94 (9.38)	NS
Serum creatinine (μmol/L)	207.45 (210.85)	135.30 (107.50)	NS
eGFR (ml/(min·1.73 m²))	22.87 (31.18)	41.35 (31.88)	NS
24-h urinary protein excretion (g)	3.51 (6.46)	2.06 (4.41)	NS
Serum total cholesterol (mmol/L)	4.47 (2.12)	4.30 (1.76)	NS
Serum triglycerides (mmol/L)	1.70 (1.56)	1.50 (1.05)	NS
LDL (mmol/L)	2.41 (1.37)	2.26 (1.76)	NS
HDL (mmol/L)	1.20 (0.56)	1.08 (0.42)	NS
24hSBPV (mmHg)	11.75±2.98	12.01 (4.22)	NS
24hDBPV (mmHg)	6.85 (2.51)	8.55 (2.99)	0.005
dSBPV (mmHg)	11.02 (3.33)	12.30 (5.76)	NS
dDBPV (mmHg)	6.63 (1.61)	8.72±2.29	0.005
nSBPV (mmHg)	8.27 (5.69)	12.86±4.13	0.005
nDBPV (mmHg)	6.87 (5.98)	9.25 (4.79)	0.049
Circadian rhythm of BP (%)	3.18 (5.97)	−0.31±8.50	NS

Data are expressed as mean±SE, number (percentage), or median (interquartile). DN: diabetic nephropathy; BMI: body mass index; CCB: calcium channel blocker; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II type 1 receptor blocker; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; HDL: high density lipoprotein; 24hSBPV: 24-h systolic BP variability; 24hDBPV: 24-h diastolic BP variability; dSBPV: daytime systolic BP variability; dDBPV: daytime diastolic BP variability; nSBPV: nighttime systolic BP variability; nDBPV: nighttime diastolic BP variability; BP: blood pressure; NS: not significant

3.2 Comparison of BP variability in DN patients with different levels of HbA1c

According to HbA1c values, the DN group was subdivided into Group A (HbA1c<7%) and Group B (HbA1c≥7%). Compared to the patients with HbA1c higher than 7%, the patients with HbA1c<7% have lower 24-h diastolic, daytime diastolic, nighttime systolic and diastolic BP variability (Table 2 and Fig. 1). There were no significant differences in age, sex, duration of diabetes, BMI, fasting blood glucose, urea nitrogen, creatinine, eGFR, total cholesterol, triglycerides, LDL, HDL, hematocrit, 24-h urinary protein excretion, antihypertensive agents, or circadian rhythm of BP between Groups A and B.

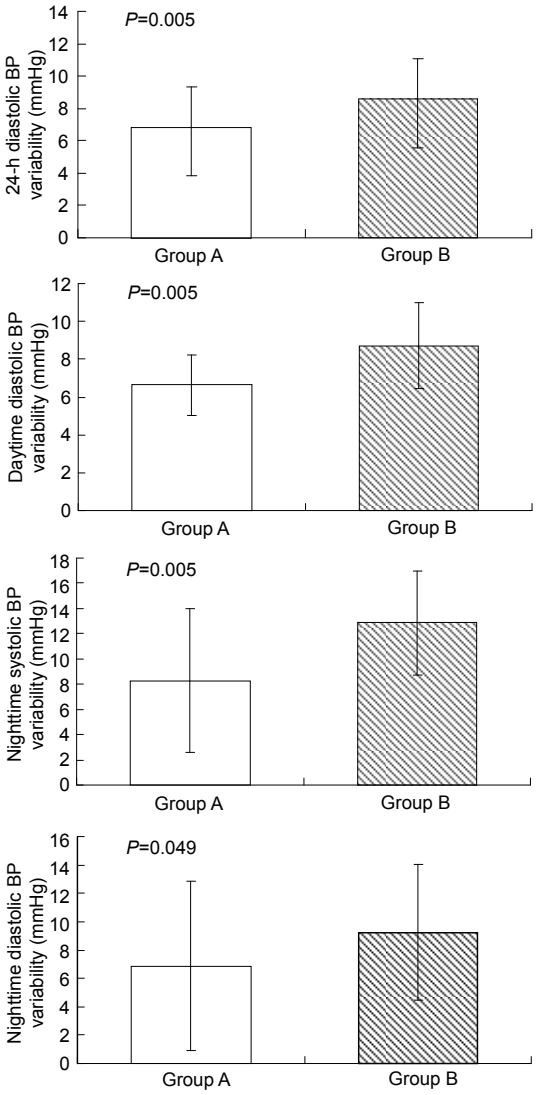

Fig. 1 Comparison of BP variability in DN patients with different levels of HbA1c

3.3 Factors affecting short-term BP variability in DN patients

To find out the factors affecting short-term BP variability in patients with DN, partial correlation analysis was performed. The followings were used as variables: age, BMI, duration of diabetes, HbA1c, urea nitrogen, creatinine, eGFR, total cholesterol, triglycerides, LDL, HDL, hematocrit, and 24-h urinary protein excretion. Partial correlation analysis revealed that age was related to 24-h systolic/diastolic BP variability and daytime diastolic BP variability. BMI was related to daytime systolic BP variability. HbA1c was related to 24-h diastolic, daytime diastolic, nighttime systolic and diastolic BP variability. Urea nitrogen was related to 24-h systolic/diastolic BP variability and daytime systolic/diastolic BP variability. eGFR was related to 24-h diastolic BP variability. Twenty-four-hour urinary protein excretion was related to daytime systolic/diastolic BP variability. Triglyceride was related to 24-h systolic/diastolic BP variability, daytime systolic/diastolic BP variability. LDL was related to 24-h systolic/diastolic BP variability, daytime systolic/diastolic BP variability.

4 Discussion

The results of this study illustrated that BP variability, particularly 24-h systolic and nighttime systolic BP variability, in patients with DN was significantly higher than that in patients with NDN, which was also accompanied with significant increases of fasting blood glucose and HbA1c. Then we suspected that the level of blood glucose was related to these differences. When compared to the patients with HbA1c≥7%, the patients with HbA1c<7% have much lower BP variability (e.g., 24-h diastolic, daytime diastolic, nighttime systolic and diastolic BP variability). We further used partial correlation analysis to reveal that HbA1c was related to short-term BP variability (e.g., 24-h diastolic, daytime diastolic, nighttime systolic and diastolic BP variability) in patients with DN.

Age, BMI, serum urea nitrogen, eGFR, 24-h urinary protein excretion, and some lipid metabolic indicators have effects on BP variability, which was shown by partial correlation analysis in Table 3. These factors have already proved their influence on BP variability in many studies, but they are not specific and cannot explain the differences between the DN group and NDN group or the differences between subgroups with different HbA1c levels when all of the data from these indicators showed no statistical difference. And these data suggested a significantly increased BP variability in patients with DN, and a potential role of HbA1c as a factor influencing BP variability level in type 2 diabetic patients with DN.

BP is subject to biological variation from heartbeat to heartbeat, breath to breath, minute to

Table 3 Factors affecting short-term BP variability in patients with diabetic nephropathy

Parameter	24hSBPV		24hDBPV		dSBPV		dDBPV		nSBPV		nDBPV	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	0.124	0.030	0.263	0.000		NS	0.233	0.000		NS		NS
Duration of diabetes		NS		NS		NS		NS		NS		NS
BMI		NS		NS	0.146	0.010		NS		NS		NS
HbA1c		NS	0.295	0.000		NS	0.324	0.000	0.463	0.042	0.233	0.000
Serum urea nitrogen	0.173	0.002	0.215	0.000	0.213	0.000	0.258	0.000		NS		NS
Serum creatinine		NS		NS		NS		NS		NS		NS
eGFR		NS	0.154	0.007		NS		NS		NS		NS
24-h urinary protein excretion		NS		NS	0.117	0.040	0.178	0.002		NS		NS
Serum total cholesterol		NS		NS		NS		NS		NS		NS
Serum triglycerides	0.310	0.000	0.251	0.000	0.349	0.000	0.307	0.000		NS		NS
LDL	0.227	0.000	0.195	0.001	0.254	0.000	0.227	0.000		NS		NS
HDL		NS		NS		NS		NS		NS		NS

BP: blood pressure; BMI: body mass index; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; HDL: high density lipoprotein; 24hSBPV: 24-h systolic blood pressure variability; 24hDBPV: 24-h diastolic blood pressure variability; dSBPV: daytime systolic blood pressure variability; dDBPV: daytime diastolic blood pressure variability; nSBPV: nighttime systolic blood pressure variability; nDBPV: nighttime diastolic blood pressure variability; NS: not significant

minute, and day to day, which is called BP variability, a quantitative index for the spontaneously physiological variation in BP, and has been documented since the 18th century. However, its clinical importance is only now being recognized. In hypertension, an increase in BP variability is a characteristic feature, and it has been proposed as a risk factor for target organ damage and to determine the efficacy of hypertension treatment, independently of absolute BP values and mean BP (Parati, 2005). It is of note that higher BP variability has been recently considered not only to give rise to left ventricular hypertrophy, intimal-medial thickness (IMT), the presence of advanced atherosclerosis, cerebral stroke and coronary heart disease, but also consistently to predict the risks of subsequent cardiovascular events and cardiovascular mortality (Kikuya *et al.*, 2000; Verdecchia *et al.*, 2007). BP is considered physiologically regulated by various complex factors (e.g., environmental stimulation, genetic factors, autonomic nervous system, augmentation of the renin-angiotensin-aldosterone system (RAS), vascular function, ageing, long-term smoking, excessive drinking, obesity, caloric overloading, emotions, inflammation, and cardiovascular control). However, the interrelationships between these factors for hypertension and BP variability are, at best, complex and are not yet well-defined.

The associations of genetic background (Kokubo *et al.*, 2006) and autonomic nervous system (Joyner *et al.*, 2008) with BP variability have received attention, especially the autonomic nervous system. BP fluctuates widely when the autonomic nervous system is absent or when key mechanisms that govern it are destroyed. However, 24-h mean arterial pressure is still surprisingly normal under these conditions (Joyner *et al.*, 2008). In recently published studies, the increase in nighttime BP variability and blunted nocturnal BP reduction are associated with sympathetic hyperactivity and elevated plasma norepinephrine in subjects with DN (Nielsen *et al.*, 1999; Tamura *et al.*, 2007), which implies an important role played by the sympathetic nervous system in the regulation of BP variability in DN patients. As is known to all, increased BP variability has been documented, related to a worse outcome, and patients of CKD, particularly on dialysis, are subject to marked BP fluctuation (Palatini, 2008). We add to those studies by showing similar findings that increased BP variability was found in the patients with DN. Meanwhile, it was significantly higher than that in NDN CKD patients with the same degree of eGFR. However, the most interesting finding was that HbA1c is strongly associated with 24-h diastolic, daytime diastolic, nighttime systolic and diastolic BP variability in the DN group, which indicates long-term glycaemic control may be a predictor of BP variability.

It is widely recognized that a substantial proportion of patients with diabetes develop diabetes complications, such as microvascular complications (retinopathy, nephropathy, and neuropathy) and CVD. Among the risk factors that have been identified, glycaemic control is perhaps one of the most important. Regarding glycaemic control and CVD, the picture is, however, less clear. There is evidence that the level of long-term glycaemia, clinically determined by HbA1c, influences the risk of CVD in patients with type 1 diabetes (Nathan *et al.*, 2005; Eeg-Olofsson *et al.*, 2010). In type 2 diabetes, the lack of benefit from improved glycaemic control on CVD outcomes in advanced diabetes has recently been debated (Kumarasamy *et al.*, 2011).

In this study, we presented evidence for the association between HbA1c and 24-h diastolic, daytime diastolic, nighttime systolic and diastolic BP variability, thereby indicating that long-term glycaemic control may be involved in cardiovascular complication in DN patients through an influence on BP variability regulation. Similarity was observed in a rat model (Kumarasamy *et al.*, 2011). However, the mechanism by which HbA1c is correlated with BP variability is somewhat unclear and needs to be considered. In theory, fluctuating long-term glycaemic control causes homeostatic imbalance, oxidative stress, impairment of the endothelial function, and more active sympathetic action, which in turn may be considered fundamental in this pathogenesis of BP variability regulation (Brownlee, 2001; Ceriello *et al.*, 2008).

Improvement of glycaemic control is clarified, associated with prevention and improvement of diabetic complications (Bronson, 2010; Cummings *et al.*, 2011) and subsequent CVD (ACCORD Study Group *et al.*, 2011; Lind *et al.*, 2011). In general, glycaemic targets for general diabetes mellitus adult population (fasting blood glucose<6.1 mmol/L, 2-h postprandial blood glucose<8.0 mmol/L, and HbA1c<7%) are

reasonable. The benefits of intensive glycaemic therapy for people with diabetes to lower the risk of developing diabetic complications and the glycaemic targets for the general diabetes mellitus adult population have been well established. For most patients with diabetes, each 1% increase of HbA1c was associated with higher risk of diabetic complications. How tightly should glycaemia be controlled in diabetic patients with overt nephropathy and renal insufficiency for optimum BP variability control? To our knowledge, the lack of related studies is obvious, and this is the first study to evaluate the relationship between HbA1c and BP variability. It suggests that poor glycaemic control is often not reasonable and may cause the risk of substantially increased BP variability in subjects with DN. Taking BP variability into special consideration, strict control with HbA1c of 7% or lower may be reasonable and acceptable for DN patients, even among individuals who have a reduced eGFR.

There are, however, also some limitations to this study. Small sample size, the lack of available data on other important risk factors such as diet, and medication adherence limit the interpretation of these results. More attention should be paid to the potential relationship of BP variability and HbA1c in DN patients, and additional large-scale, long-term prospective clinical trials are needed for better understanding.

In conclusion, we showed in this observational setting that significantly higher BP variability was seen in the DN group. This study, for the first time, demonstrated the possible relationship between glycaemic control and BP variability in DN patients and provided the fundamental basis for further studies.

Compliance with ethics guidelines

Fang LIU, Min WU, Yan-huan FENG, Hui ZHONG, Tian-lei CUI, You-qun HUANG, Ya-ping LIANG, Yong-shu DIAO, Li ZANG, Ling LI, Jing ZANG, Hong-yu QIU, Song-min HUANG, and Ping FU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

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