Hypertension Research (2015) 38, 193–198

www.nature.com/hr

ORIGINAL ARTICLE

The relationships between visit-to-visit blood pressure variability and renal and endothelial function in chronic kidney disease

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Visit-to-visit blood pressure variability has been shown to be an independent risk factor for cardiovascular diseases. High visit-to-visit blood pressure variability and endothelial dysfunction are observed in patients with chronic kidney disease. It is therefore assumed that high variability in visit-to-visit blood pressure measurements may be associated with endothelial dysfunction in these patients. The present study investigated the associations between visit-to-visit blood pressure variability and renal and endothelial function in patients with chronic kidney disease. We analyzed 150 consecutive patients with predialysis chronic kidney disease who visited our outpatient clinic from January 2006 to December 2010. The study examined the relationships between variability in visit-to-visit systolic blood pressure levels or mean systolic blood pressure (M SBP) and estimated glomerular filtration rate (eGFR) and flow-mediated dilation, an index of endothelial function. Variability in visit-to-visit systolic blood pressure showed a significant negative association with eGFR, independent of age, hemoglobin A1c, low-density lipoprotein (LDL) cholesterol and uric acid, whereas M SBP did not. Similarly, variability in SBP showed a significant negative association with flow-mediated dilation, independent of age, eGFR, HbA1c, LDL cholesterol and M SBP. These data indicate that variability in visit-to-visit blood pressure measurements is associated with impaired renal and endothelial function in patients with chronic kidney disease. This finding suggests that reducing blood pressure fluctuations might have beneficial effects in patients with chronic kidney disease, although this point needs to be addressed by future studies.
Hypertension Research (2015) **38,** 193–198; doi:10.1038/hr.2014.163; published online 4 December 2014

Keywords: chronic kidney disease; glomerular filtration rate; cardiovascular disease; endothelial function

INTRODUCTION

Chronic kidney disease (CKD) is characterized by high morbidity and mortality associated with cardiovascular diseases.[1] CKD is a heterogeneous group of disorders caused by multiple factors such as hypertension, poor glycemic control, abnormalities in calcium and phosphate metabolism, endothelial dysfunction and anemia.[2–5] Of these, hypertension is regarded as the most common and potentially treatable risk factor. Recent studies have shown that not only absolute blood pressure (BP) levels, but also fluctuations in these levels have a significant impact on end-organ damage.[6,7] Fluctuations in BP include beat-to-beat, day-to-day and visit-to-visit variability, and circadian and seasonal variations. These fluctuations are influenced by vascular, neurohumoral and environmental factors.

The prognostic significance of visit-to-visit BP variability (BPV) has recently been proposed. Rothwell *et al.*[8] showed that this variability is a strong predictor of stroke, independent of mean systolic BP (SBP) in treated hypertensive patients. Nagai *et al.*[9] also showed a significant correlation between visit-to-visit BPV and indices of atherosclerosis including carotid intima-media thickness and arterial stiffness. It can therefore be assumed that visit-to-visit BPV is associated with atherosclerosis.[10] Endothelial dysfunction is considered to be the initial pathogenic event of atherosclerosis and is a risk factor for cardiovascular disease.[11,12] Keith *et al.*[13] showed that higher visit-to-visit BPV was associated with endothelial dysfunction in African Americans, and suggested that endothelial dysfunction may be the link between visit-to-visit BPV and atherosclerosis.

High visit-to-visit BPV[14–16] and endothelial dysfunction[17] have been reported in CKD patients. This suggests that there may be an association between these two factors in these patients. However, this possibility remains speculative. The present study therefore investigated the associations between visit-to-visit BPV and renal and endothelial function in CKD patients.

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Received 22 June 2014; revised 21 September 2014; accepted 27 September 2014; published online 4 December 2014

METHODS

Subjects

We studied consecutive predialysis CKD patients who regularly visited our outpatient clinic at least 10 times between January 2006 and December 2010. All the participants were enrolled after informed consent was obtained. The study was approved by the ethical committee of Kansai Medical University Hirakata Hospital. The diagnosis of CKD was made according to the criteria of K/DOQI as kidney damage for $\geqslant 3$ months, defined as structural or functional abnormalities of the kidney, with or without a decrease in estimated glomerular filtration rate (eGFR), manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests with an eGFR < 60 ml min^{-1} 1.73 m^{-2} for $\geqslant 3$ months, with or without kidney damage.[18] Patients were excluded if their observation period was <12 months. Patients who had suffered from ischemic heart disease, acute coronary syndrome, congestive heart failure (New York Heart Association class II or greater) or stroke within 6 months of the start of the study, or who were pregnant, were also excluded from the study. The patients underwent BP measurements at every outpatient visit. Biochemical examination of the blood and urine was carried out on some occasions.

Measurements of BP

BP was measured at every outpatient clinic visit with the patient in the sitting position after at least 5 min of rest. The values were determined using an automated oscillometric sphygmomanometer (MPV3301, Nihon Kohden, Tokyo, Japan). The first reading at each visit was used in the study. In addition to mean systolic BP (M SBP), visit-to-visit BPV was calculated as the s.d. (SD SBP), coefficient of variation (=SD SBP/M SBP, CV SBP) and Δ (= maximum systolic BP-minimum systolic BP, Δ SBP), based on systolic BP values from 10 consecutive visits.

Urinary examinations

A spot urine sample was obtained at the clinic visit. Urine creatinine and protein were measured using the turbidimetric immunoassay method. The urine protein-creatinine ratio (mg g^{-1}·Cr) was calculated by dividing urinary protein by urinary creatinine concentration.

Biochemical evaluation

The serum concentrations of creatinine and low-density lipoprotein (LDL) cholesterol, uric acid and hemoglobin A1c-Japan Diabetes Society (HbA1c-JDS) were measured using standard laboratory methods. eGFR (min^{-1} 1.73 m^{-2}) was calculated as: 194 x creatinine$^{-1.094}$ age$^{-0.287}$ (×0.739 if female).[19]

Table 1 Baseline characteristics of the patients

Measure	*Mean ± s.d.*
N	150
Age (year)	62.7 ± 11.7
Female (%)	40.6
eGFR (ml min^{-1} 1.73 m^{-2})	38.6 ± 25.4
Urinary protein excretion (mg g^{-1}·Cr)	1939.3 ± 3160.1
Smoking (%)	26
Anti-diabetic therapy (%)	37.3
Hemoglobin A1c (%)	5.9 ± 1.1
Lipid-lowering therapy (%)	44.6
LDL cholesterol (mg dl^{-1})	119.4 ± 41.2
Uric acid (mg dl^{-1})	6.5 ± 1.6
M SBP (mm Hg)	128.6 ± 13.2
SD SBP (mm Hg)	14.3 ± 5.8
CV SBP	0.111 ± 0.040
⊿ SBP (mm Hg)	45.3 ± 19.0
FMD (%)	5.2 ± 3.3
NMD (%)	12.5 ± 6.5

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilatation; LDL, low-density lipoprotein; M, mean; NMD, nitroglycerin-mediated dilatation; SBP, systolic blood pressure.

Measurements of flow-mediated dilatation and nitroglycerin-mediated dilatation

The percent changes in brachial artery diameter were calculated in response to increased flow-mediated vasodilation (FMD), an index of endothelium-dependent function, and nitroglycerin-mediated dilation (NMD), an index of endothelium-independent function, as described previously.[20,21] The right arm of the participant was comfortably immobilized in the extended position, allowing for ultrasound scanning of the brachial artery 5–10 cm above the antecubital fossa. Baseline images of the right brachial artery were first obtained using a UNEXEF38G (Unex Corporation, Nagoya, Japan). After the baseline images had been recorded, reactive hyperemia was induced by distal occlusion of the vessel in the right forearm distal to the antecubital fossa using a cuff inflated to suprasystolic pressure (usually SBP +70 mm Hg) for 5 min. After at least 15 min of rest, a second series of baseline images were obtained, followed by sublingual administration of a 0.075 mg nitroglycerin tablet to assess endothelium-independent vasodilation.

Study protocols

The relationships between M SBP, SD SBP, CV SBP or ΔSBP and age, smoking habit, anti-diabetic therapy, HbA1c, lipid-lowering therapy, LDL cholesterol, uric acid and eGFR were examined. The relationships between FMD or NMD and age, smoking habit, eGFR, anti-diabetic therapy, HbA1c, lipid-lowering therapy, LDL cholesterol, uric acid, M SBP, SD SBP, CV SBP and ΔSBP were also investigated.

Statistical analysis

All data were expressed as mean ± s.d. Single linear regression analyses were used to investigate the relationships between visit-to-visit BPV and eGFR, FMD or NMD. Multiple linear regression analyses were performed to determine the factors that affected eGFR, FMD or NMD. Analysis of variance was used to identify differences between each antihypertensive treatment group. The level of significance was defined as $P<0.05$. All statistical analyses were performed using StatView 5.0 statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the study subjects

A total of 150 patients were enrolled in the study. The clinical and endothelial parameters of the study subjects are summarized in Table 1. M SBP was 128.6 ± 13.2 mm Hg. Angiotensin receptor blockers were administered in 76.0% of the patients, angiotensin-converting enzymes inhibitors in 4.6%, calcium channel blockers in 50.6%, diuretics in 29.3%, β-blockers in 4.6% and α-blockers in 4.6%. Twenty-seven percent of patients were treated with 1 antihypertensive agent, 40.6% with 2 agents and 18.0% with 3 or more agents. M SBP, SD SBP, CV SBP and ΔSBP were not significantly different between each treatment group.

Correlation between BP levels and eGFR

Single linear regression analyses showed a significant negative correlation between eGFR and uric acid, SD SBP, CV SBP and Δ SBP, and a significant positive relationship between eGFR and LDL cholesterol (Table 2). The multiple linear regression analyses using SD SBP (model 1), CV SBP (model 2) and Δ SBP (model 3) showed significant associations with eGFR after adjustment for age, HbA1c, LDL cholesterol, uric acid and M SBP (Table 3).

Correlation between BP levels and flow-mediated dilatation and nitroglycerin-mediated dilatation

The single linear regression analyses showed a significant negative relationship between FMD and age, M SBP, SD SBP, CV SBP and Δ

SBP and a significant positive relationship between FMD and eGFR (Table 4). Multiple linear regression analysis showed M SBP (model 1) was significantly associated with FMD after adjustment for age, eGFR, HbA1c and LDL cholesterol, and SD SBP (model 2) and Δ SBP (model 4) were significantly associated with FMD after adjustment for age, eGFR, HbA1c, LDL cholesterol and M SBP (Table 5).

Single linear regression analyses also showed a significant negative correlation between NMD and age, anti-diabetic therapy and M SBP (Table 6). As shown in Table 7, multiple linear regression analysis demonstrated a significant association of NMD adjusted for age, eGFR, HbA1c and LDL cholesterol with M SBP (model 1), but not adjusted for age, eGFR, HbA1c, LDL cholesterol and M SBP with SD SBP (model 2), CV SBP (model 3) or Δ SBP (model 4).

DISCUSSION

The present study demonstrated two major findings regarding visit-to-visit BPV in CKD patients. First, visit-to-visit BPV was associated negatively with eGFR independent of age, HbA1c, LDL cholesterol, uric acid and M SBP. Second, visit-to-visit BPV was associated negatively with FMD, independent of age, eGFR, HbA1c, LDL cholesterol and M SBP. These results suggested that visit-to-visit BPV may be associated with impaired renal and endothelial function in CKD patients.

Correlation between visit-to-visit BPV and eGFR

Eric *et al.*[14] reported that both visit-to-visit BPV and mean BP were independent predictors for the risk of developing albuminuria in patients with type 1 diabetes. Similarly, Yokota *et al.*[16] reported that visit-to-visit BPV correlated significantly with the annual decline of eGFR in patients with non-diabetic CKD. Our data are in accordance with these findings as we showed indices of visit-to-visit BPV correlated negatively with eGFR, independent of age, HbA1c, LDL cholesterol, uric acid and M SBP in patients with CKD (Table 3). We therefore consider that high visit-to-visit BPV is associated with renal dysfunction. In contrast, there was no relationship between SD SBP, CV SBP or Δ SBP and urinary protein (data not shown).

Interestingly, M SBP did not show a significant relationship with eGFR, raising the possibility that visit-to-visit BPV is more strongly associated with eGFR than average values of office BP. It is possible that instability in intrarenal hemodynamics caused by visit-to-visit BPV may initiate renal damage. It is also possible that the instability of fluid volume and/or vasoconstriction caused by renal dysfunction may increase visit-to-visit BPV. However, these presumptions are not validated and future studies are therefore required to determine the mechanisms of this association.

Table 2 Single linear regression analysis with eGFR

	r	P *value*
Age (year)	−0.151	0.064
Smoking (+) = 1, (−) =0	−0.15	0.067
Anti-diabetic therapy (+) = 1, (−) =0	−0.087	0.288
Hemoglobin A1c (%)	0.06	0.488
Lipid-lowering therapy (+) = 1, (−) =0	−0.083	0.31
LDL cholesterol (mg dl^{-1})	0.218	0.013
Uric acid (mg dl^{-1})	−0.605	<0.001
M SBP (mm Hg)	−0.089	0.281
SD SBP (mmHg)	−0.258	0.001
CV SBP	−0.269	<0.001
⊿ SBP (mm Hg)	−0.28	<0.001

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; M, mean; SBP, systolic blood pressure.

Table 4 Single linear regression analysis with FMD

	r	P *value*
Age (year)	−0.34	<0.001
Smoking (+) = 1, (−) = 0	−0.112	0.17
eGFR (ml min^{-1} 1.73 m^{-2})	0.256	0.001
Anti-diabetic therapy (+) = 1, (−) = 0	−0.154	0.059
Hemoglobin A1c (%)	−0.056	0.519
Lipid-lowering therapy (+) = 1, (−) = 0	0.085	0.301
LDL cholesterol (mg dl^{-1})	−0.025	0.782
Uric acid (mg dl^{-1})	−0.144	0.077
M SBP (mm Hg)	−0.262	0.001
SD SBP (mm Hg)	−0.302	<0.001
CV SBP	−0.229	0.004
⊿ SBP (mm Hg)	−0.294	<0.001

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; LDL, low-density lipoprotein; M, mean; SBP, systolic blood pressure.

Table 3 Multiple linear regression analysis with eGFR

	Model 1		*Model 2*		*Model 3*	
	β	P *value*	β	P *value*	β	P *value*
Age (year)	−0.14	0.054	−0.138	0.055	−0.137	0.057
Hemoglobin A1c (%)	0.117	0.121	0.12	0.107	0.11	0.144
LDL cholesterol (mg dl^{-1})	0.06	0.411	0.054	0.455	0.046	0.531
Uric acid (mg dl^{-1})	−0.566	<0.001	−0.562	<0.001	−0.555	<0.001
M SBP (mm Hg)	−0.019	0.821	−0.058	0.449	−0.001	0.99
SD SBP (mm Hg)	−0.165	0.04	—	—	—	—
CV SBP	—	—	−0.181	0.015	—	—
⊿ SBP (mm Hg)	—	—	—	—	−0.2	0.015
	R^2 = 0.431		R^2 = 0.440		R^2 = 0.406	
	P <0.05		P <0.05		P <0.05	

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; M, mean; SBP, systolic blood pressure.

Table 5 Multiple linear regression analysis with FMD

	Model 1		*Model 2*		*Model 3*		*Model 4*	
	β	P *value*	β	P *value*	β	P *value*	β	P *value*
Age (year)	−0.317	<0.001	−0.309	<0.001	−0.312	<0.001	−0.31	<0.001
eGFR (ml min^{-1} 1.73 m^{-2})	0.14	0.11	0.092	0.302	0.093	0.299	0.079	0.38
Hemoglobin A1c (%)	−0.036	0.687	−0.046	0.598	−0.039	0.656	−0.05	0.563
LDL cholesterol (mg dl^{-1})	−0.118	0.173	−0.137	0.111	−0.136	0.115	−0.15	0.083
M SBP (mm Hg)	-0.193	0.032	−0.109	0.256	−0.167	0.062	−0.099	0.305
SD SBP (mm Hg)	—	—	−0.204	0.033	—	—	—	—
CV SBP	—	—	—	—	−0.165	0.065	—	—
⊿ SBP (mm Hg)	—	—	—	—	—	—	−0.223	0.024
	$R^2=0.194$		$R^2=0.225$		$R^2=0.218$		$R^2=0.229$	
	$P<0.05$		$P<0.05$				$P<0.05$	

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; LDL, low-density lipoprotein M, mean; SBP, systolic blood pressure.

Table 6 Single linear regression analysis with NMD

	r	P *value*
Age (year)	−0.387	<0.001
Smoking (+) = 1, (−) = 0	–0.099	0.242
eGFR (ml min^{-1} 1.73 m^{-2})	0.162	0.055
Anti-diabetic therapy (+) = 1, (−) = 0	–0.221	0.008
Hemoglobin A1c (%)	−0.161	0.067
Lipid-lowering therapy (+) = 1, (−) = 0	0.057	0.505
LDL cholesterol (mg dl^{-1})	0.063	0.488
Uric acid (mg dl^{-1})	−0.162	0.055
M SBP (mm Hg)	−0.292	<0.001
SD SBP (mm Hg)	−0.118	0.164
CV SBP	−0.049	0.562
⊿ SBP (mm Hg)	−0.133	0.116

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; M, mean; NMD, nitroglycerin–mediated dilatation; SBP, systolic blood pressure.

Correlation between visit-to-visit BPV and FMD and NMD

FMD reflects augmented synthesis of nitric oxide (NO) from endothelial cells in response to increased vascular flow following cuff-release. There is evidence that such vascular dilatation responses are mediated through not only NO synthesis, but also by smooth muscle function. Endothelium-derived NO stimulates guanylyl cyclase (GC) activity, leading to further reduction in vascular tone.[22] It is therefore considered that FMD is mediated by serial interactions between endothelial and smooth muscle cells. In contrast, NMD measures the ability of vascular relaxation following administration of nitroglycerin, which directly reduces smooth muscle tonus *via* intrinsic GC activation independent of endothelial NO pathways. It is therefore generally thought that NMD depends mainly on nitroglycerin-induced smooth muscle function, and that the contribution of endothelial function is almost negligible.

In a study of 36 African Americans, Diaz *et al.*[13] showed that higher visit-to-visit BPV (SD SBP and CV SBP) was associated with a lower FMD/NMD ratio, independent of age, body mass index and mean BP levels. Our finding of a significant negative association between visit-to-visit BPV and FMD (Table 4) in Japanese patients was in accordance with their study, although this is the first report to show an association between visit-to-visit BPV and endothelial dysfunction in CKD patients.

Long-term elevation in BP causes endothelial dysfunction,[23] whereas antihypertensive treatment restores normal function.[24] However, the present study showed that M SBP failed to show a significant association with FMD after adjustment for age, eGFR, HbA1c and LDL cholesterol, and indices of visit-to-visit BPV (Table 5). In contrast, indices of visit-to-visit BPV were associated significantly with FMD even after adjustment for these factors. These data suggest that visit-to-visit BPV may be more strongly associated with endothelial function than average values of office BP, similar to the relationships seen with renal function. The reason why visit-to-visit BPV is associated with endothelial dysfunction needs to be considered. Eto *et al.*[25] showed that increased BPV, independent of average BP level, impaired endothelial function by inhibiting NO production and enhancing neointimal formation, thereby contributing to atherogenesis in rats. In contrast, it has been proposed that endothelial dysfunction may cause high BPV.[26] It is therefore possible that visit-to-visit BPV and endothelial dysfunction affect each other. One hypothesis is that renal dysfunction may cause endothelial dysfunction, that in turn, increases visit-to-visit BPV. However, in the present study, indices of visit-to-visit BPV (SD SBP, Δ SBP) were associated significantly with FMD even after adjustment for eGFR (Table 5). This suggested that the relationship between visit-to-visit BPV and endothelial dysfunction may not be due to renal dysfunction, although this presumption cannot be completely excluded. Further studies are needed to determine the mechanism by which visit-to-visit BPV is associated with impaired endothelial function in CKD patients.

Comparisons of effects of antihypertensive drugs on visit-to-visit BPV

Rothwell *et al.*[27] reported that calcium channel blockers and β-blockers had different effects on visit-to-visit BPV in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) study. This study compared the effects of the two agents in hypertensive patients. In contrast, the present study showed that indices of visit-to-visit BPV were not significantly different between treatment groups. The reason for this discrepancy is unclear, although it may be due to the different antihypertensive agents used. For example, in our study renin-angiotensin system, inhibitory drugs were administered to 76.0% of patients, whereas only 4.6% of patients were taking a β-blocker. Furthermore, many patients were

Table 7 Multiple linear regression analysis with NMD

	Model 1		*Model 2*		*Model 3*		*Model 4*	
	β	P *value*	β	P *value*	β	P *value*	β	P *value*
Age (year)	−0.3	<0.001	−0.301	<0.001	−0.302	<0.001	−0.302	<0.001
eGFR (ml min^{-1} 1.73 m^{-2})	0.071	0.42	0.084	0.358	0.087	0.344	0.08	0.332
Hemoglobin A1c (%)	−0.127	0.16	−0.125	0.166	−0.126	0.164	−0.125	0.169
LDL cholesterol (mg dl^{-1})	−0.023	0.788	−0.019	0.832	−0.017	0.843	−0.019	0.831
M SBP (mm Hg)	−0.237	0.009	−0.26	0.01	−0.247	0.008	−0.251	0.014
SD SBP (mm Hg)	—	—	0.052	0.601	—	—	—	—
CV SBP	—	—	—	—	0.055	0.5487	—	—
⊿ SBP (mm Hg)	—	—	—	—	—	—	0.031	0.764
	$R^2=0.219$ $P<0.05$		$R^2=0.221$		$R^2=0.222$		$R^2=0.220$	

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; M, mean; NMD, nitroglycerin–mediated dilatation; SBP, systolic blood pressure.

administered two or more different antihypertensive agents and it is possible that this may have also affected the results. Comparison of each antihypertensive agent independently is therefore necessary in future studies.

Study limitations

Several limitations of the present study warrant mention. Firstly, because of the cross-sectional design of the study, it was difficult to ascertain whether high visit-to-visit BPV preceded impaired kidney and endothelial function or vice versa. In addition, the relationship between past long-term average BP value and eGFR cannot be determined because M SBP calculated in this study reflects just the average of current BP. Secondly, the number of patients tested was relatively small. Thirdly, although we measured BP in 10 consecutive visits for more than 12 months, the effects of seasonal variation in BP on visit-to-visit BPV cannot be excluded. There is evidence that seasonal variation in BP is higher during winter than in the summer.[28] Larger-scale prospective trials are needed to better assess the causal relationships between alterations in visit-to-visit BPV and progression of renal dysfunction or endothelial dysfunction in CKD patients.

CONCLUSION

In conclusion, our data suggest that visit-to-visit BPV is associated with impaired renal and endothelial function in CKD patients. It is possible that reduction of BP fluctuations is required as a major goal of anti-hypertensive treatment in CKD patients. Intervention studies of methods for reducing visit-to-visit BPV are required to validate this hypothesis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

No part of our work has been published or is under consideration for publication elsewhere. We have no disclaimers to declare.

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