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Analysis of Factors Relating to Day-to-day Home Blood Pressure Variation in Hypertensive Patients

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SUMMARY

In order to prevent cardiovascular events and organ injuries in hypertensive patients, strict blood pressure (BP) control over 24 hours is of utmost importance. In addition to the BP level, it has been indicated that the variabilities of blood pressure during a day or between visits also influence the risk of cardiovascular disorders. This study aimed to delineate the factors relating to the variations of office and home BPs throughout a year in hypertensive outpatients under antihypertensive therapy. The office BP value (131/77 mmHg) was comparable to the morning home BP (130/76), but was higher compared to the evening home BP (126/73), however, the coefficient of variation (CV) values were comparable between the office and the home BPs. Correlations of BP and CV were stronger between the morning and the evening home BPs than between the office and the home BPs. The CV of systolic office BP was greater in patients with diabetes mellitus than the patients without diabetes (7.8 vs 6.1%). In patients with chronic kidney disease, the CVs of diastolic office BP and evening home BP were greater than the patients without chronic kidney disease (8.0 vs 6.2% and 8.1 vs 6.7%, respectively). In addition, The CVs of diastolic morning and evening home BP were positively correlated with serum creatinine and a negatively correlated with estimated glomerular filtration rate. Patients with cardiovascular diseases such as stroke and coronary artery disease showed greater CV of diastolic morning home BP than the patients without cardiovascular diseases (8.2 vs 6.6%). These results suggest that the home BP exhibits different variability from the office BP, and the BP variability is increased in high-risk hypertensive patients with diabetes mellitus, chronic kidney disease or cardiovascular diseases.

Key words : hypertension, home blood pressure, blood pressure variation

INTRODUCTION

Cardiovascular diseases such as stroke and coronary artery disease are the major cause of death worldwide alongside cancers and infectious diseases. In addition, cardiovascular organ failures such as heart failure and renal failure impair physical and mental activities, thereby reducing social productivity. These cardiovascular diseases and organ dysfunctions occur based on the development of arteriosclerosis which is promoted by aging, smoking and lifestyle-related diseases such as hypertension, diabetes mellitus and dyslipidemia. Among these risk factors of cardiovascular diseases, hypertension exerts major effects on the development of arteriosclerosis and the incidence of cardiovascular diseases. Therefore, the antihypertensive therapy is of utmost importance to inhibit the incidence of cardiovascular diseases and

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organ failures in hypertensive patients. In fact, according to the meta-analysis of clinical studies, 10 mmHg lowering of systolic blood pressure (BP) is associated with 30-40% reduction in stroke and 20-30% reduction in coronary artery disease[1,2].

Hypertension is generally defined as BP levels of 140/90 mmHg or higher. Meta-analysis of epidemiological studies shows lower systolic and diastolic BP levels are associated with lower risk of cardiovascular diseases such as stroke and ischemic heart diseases in wide range of age strata, and this relationship can be observed even in the normotensive range below 140/90 mmHg to the level as low as 115/75 mmHg[3]. In the clinical practice, antihypertensive therapy is generally performed based on the office BP values, however, the out-of-office BPs such as ambulatory BP and home BP have been shown to be more predictive of the incidence of cardiovascular diseases and cardiovascular organ injuries than office BP. Furthermore, it has been reported that other than BP values, the variabilities of BP such as diurnal changes and visit-to-visit variations are associated with the risk of developing cardiovascular diseases and organ injuries[4,5]. In this respect, it seems there is insufficient information indicating the day-to-day variation of home BP and its relations to the cardiovascular disorders.

In this study, the variations of office and home BPs throughout the year were evaluated in hypertensive out-patients under antihypertensive treatment, and the factors relating to these BP variations were analyzed.

METHODS

In this study, 83 hypertensive out-patient subjets who recorded their home blood pressure measurements were enrolled. We excluded any patients with poorly controlled hypertension which exceeded 160/100 mmHg or there was a secondary cause of hypertension other than chronic kidney disease (CKD). However, patients undergoing renal replacement therapy were not included in this study. In addition, we excluded any patients who developed cardiovascular events during the year BP data were collected or any patients who had poor adherence to antihypertensive medication.

BP records were collected during the year of 2016 (57 patients) and 2017 (26 patients) in which the prescriptions of antihypertensive drugs were not changed. Office BP was measured with a sphygmomanometer for 1-2 times in the sitting position after resting for at least 20 min at each visit every 4 to 8 weeks. The average value was calculated and used for the analyses whenever the office BP was measured twice during visits. The average number of visits was 8.2 times per year. Home BP was measured every day using an arm-cuff oscillometric automatic manometer within 1 hour of awakening (before taking drugs) as morning blood pressure and before going to bed as evening blood pressure. All the home BP records within 7 days before each visit were collected for the analyses. The home BP was also measured 1-2 times and the average value was recorded whenever the measurement was repeated twice. The patients used their own manometers equipped with arm cuffs. The data of office BP and home BP were collected from all 83 participants. In addition to calculating the average value of office BP, the coefficient of variation (CV) was calculated as percent value of the standard deviation (SD) to the mean. The average and CV were also calculated for morning and evening home BP.

Blood samples were obtained after overnight fasting during the year in which blood pressure data were recorded. The samples were served for the measurements of blood cell counts and routine blood chemistry including liver enzymes, total protein, albumin, renal function, uric acid, electrolytes, lipids, glucose and hemoglobin A1c. Serum LDL cholesterol was calculated by the Friedewald's formula[6] : LDL cholesterol = total cholesterol − HDL cholesterol − (triglycerides $\times 0.2$). The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine level and age by the following equation[7] : $eGFR = 194 \times Age^{-0.287} \times sCr^{-1.094}$ ($\times 0.739$ for females). Casual urine samples were also collected during the year for the evaluation of proteinuria.

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects and was approved by the institutional review board. Informed consent was obtained from all subjects after explaining the study objective and design.

Table 1 Background characteristics of the study subjects

Age, years	68.3±10.5
Gender, male/female	34/49
Body mass index, kg/m^2	22.3±3.7
Complications	
Diabetes mellitus	23 (27.7%)
Dyslipidemia	37 (44.6%)
Hyperuricemia	29 (34.9%)
Cardiovascular disease	24 (28.9%)
Chronic kidney disease	48 (57.8%)

Data are the mean±SD.

Table 2 Antihypertensive medications and other drugs given in the 83 patients

Drug	Number of patients	Percentage
Antihypertensive drug		
Diuretic	13	15.7%
β blocker	11	13.3%
Calcium channel blocker	56	67.5%
ARB	61	73.5%
ACEI	3	3.6%
Other	16	19.3%
Anti-diabetic drug	16	19.3%
Lipid-lowering drug	37	44.6%
Antihyperuricemic drug	15	18.1%
Anti-anginal drug	9	10.8%
Anti-platelet drug	20	24.1%

ARB : angiotensin II receptor blocker, ACEI : angiotensin converting enzyme inhibitor.

Clinical data were expressed as means±standard deviations (SD). Values between the 2 groups were compared by t-test, however, Wilcoxon test was applied for the data with skewed distribution. Comparisons of 3 groups were performed using analysis of variance (ANOVA) followed by Dunnett's t-test for post-hoc between group comparisons. Correlations between the two variables were analyzed by linear regression analysis. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

The background characteristics of study subjects are shown in Table 1. Lifestyle related diseases other than hypertension such as diabetes mellitus, dyslipidemia and hyperuricemia are complications in 27.7%, 44.6% and 34.9% of the patients, respectively. In addition, 24 patients have complications with cardiovascular diseases (CVD) such as cerebrovascular disease (n=3), coronary artery disease (n=11), valvular heart disease (n=2), arrhythmia (n=8) and peripheral artery disease (n=3). Three patients had two cardiovascular diseases. Forty-eight patients corresponded to CKD defined as eGFR less than 60 mL/min/1.73 m^2 or proteinuria. The causes of CKD were diabetic nephropathy (n=16), chronic glomerulonephritis (n=15), nephrosclerosis (n=14), chronic pyelonephritis (n=1), lupus nephritis (n=1) and drug-induced nephropathy (n=1).

Table 2 shows the drugs given to the patients. As an antihypertensive medication, calcium channel blockers (CCB) and angiotensin II receptor blockers (ARB) were most frequently used. These antihypertensive medications were not changed during the year in which the office and home blood pressure data were collected. In addition, drugs for lifestyle-related diseases were administered to respective patients with diabetes mellitus. dyslipidemia and hyperuricemia.

The laboratory findings of study subjects were listed in Table 3. Although some of the patients had complication with diabetes mellitus, dyslipidemia and hyperuricemia, they were treated with respective medications indicated in Table 2 and the average values of blood glucose, hemoglobin A1c, serum lipids and uric acid were in the normal ranges. Among the 48 patients with CKD, 46 showed eGFR less than 60 mL/min/1.73 m^2 and 27 showed proteinuria. Therefore, the averaged serum creatinine was higher and the averaged eGFR was lower than the normal range in the total study subjects.

Table 4 shows the average values and CV of office and home BP and heart rate (HR). Average systolic and diastolic office BPs were comparable to morning home BP but were higher compared to the evening home BP ($p=0.011$ for systolic BP and $p=0.005$ for diastolic BP). Accordingly, systolic and diastolic values of morning home BP were higher than those of eve-

Table 3 Laboratory data of the study subjects

Blood chemistry		Blood cell count	
AST, U/L	22±6	WBC, $\times 10^3$/mm^3	6.26±2.02
ALT, U/L	18±8	RBC, $\times 10^4$/mm^3	427±57
Total protein, g/dL	7.1±0.5	Hemoglobin, g/dL	12.8±1.6
Albumin, g/dL	4.1±0.3	Hematocrit, %	39.3±4.6
Uric acid, mg/dL	5.7±1.4	Platelet, $\times 10^4$/mm^3	24.7±7.1
Creatinine, mg/dL	1.28±1.10		
eGFR, mL/min/1.73 m^2	54.5±25.5	Urinalysis	
Glucose, mg/dL	105±21		
Hemoglobin A1c, %	5.9±0.5	Proteinuria, +/−	27/56
HDL cholesterol, mg/dL	60±16		
LDL cholesterol, mg/dL	117±30		
Triglycerides, mg/dL	139±73		

Mean±SD. AST : aspartate transaminase, ALT : alanine transaminase, eGFR : estimated glomerular filtration rate, HDL : high-density lipoprotein, LDL : low-density lipoprotein, WBC : white blood cell, RBC : red blood cell.

Table 4 Average values and coefficient of variations of office blood pressure and morning and evening home blood pressure

	Average value	Coefficient of variation, %
Office blood pressure		
Systolic, mmHg	130.7±12.5	7.2±2.6
Diastolic, mmHg	76.9±9.2	7.4±2.8
Heart rate, bpm	72.0±10.3	7.3±2.9
Morning home blood pressure		
Systolic, mmHg	130.4±10.2	6.1±2.1
Diastolic, mmHg	76.0±8.9	7.0±2.8
Heart rate, bpm	69.1±9.6	7.3±3.6
Evening home blood pressure		
Systolic, mmHg	126.1±10.0	6.5±2.2
Diastolic, mmHg	73.0±8.2	7.7±2.8
Heart rate, bpm	70.2±9.4	7.2±2.6

Mean±SD.

ning home BP ($p=0.017$ and $p=0.035$, respectively). As for CV, significant differences were not observed among the office and the home BPs.

Table 5 shows the correlations between office and home measurements of BP and HR. Either systolic or diastolic BP, the correlations were closer between the morning and the evening home BPs than between the office BP and the morning or the evening home BP. Also the correlations of HR values were closer between the morning and the evening home measurements than between the office and the home measurements. With regards to the correlations of CV values between the office and the home measurements, as shown in Table 6, the CV of systolic office BP did not have significant correlation with the CV of morning or evening home systolic BP. The correlation of CV of HR was also closer between the morning and the evening home measurements than between the office and the home measurements.

Figure 1A depicts the office and the home BPs between patients with or without diabetes mellitus. The diabetic patients had lower diastolic office BP than the non-diabetic patients, however, the diastolic home BP in the morning or evening did not differ

Table 5 Correlations between the averaged values of blood pressure and heart rate

	Office-Morning		Office-Evening		Morning-Evening	
	r	P value	r	P value	r	P value
Systolic BP	0.333	0.0022	0.352	0.0022	0.818	<0.0001
Diastolic BP	0.548	<0.0001	0.492	<0.0001	0.879	<0.0001
Heart rate	0.762	<0.0001	0.752	<0.0001	0.914	<0.0001

BP : blood pressure, r : correlation coefficient.

Table 6 Correlations between the coefficient of variation of blood pressure and heart rate values

	Office-Morning		Office-Evening		Morning-Evening	
	r	P value	r	P value	r	P value
Systolic BPV	0.217	0.0504	0.087	0.4653	0.619	<0.0001
Diastolic BPV	0.354	0.0011	0.233	0.0489	0.552	<0.0001
HRV	0.250	0.0339	0.168	0.1787	0.528	<0.0001

BPV : blood pressure variation, HRV : heart rate variation, r : correlation coefficient.

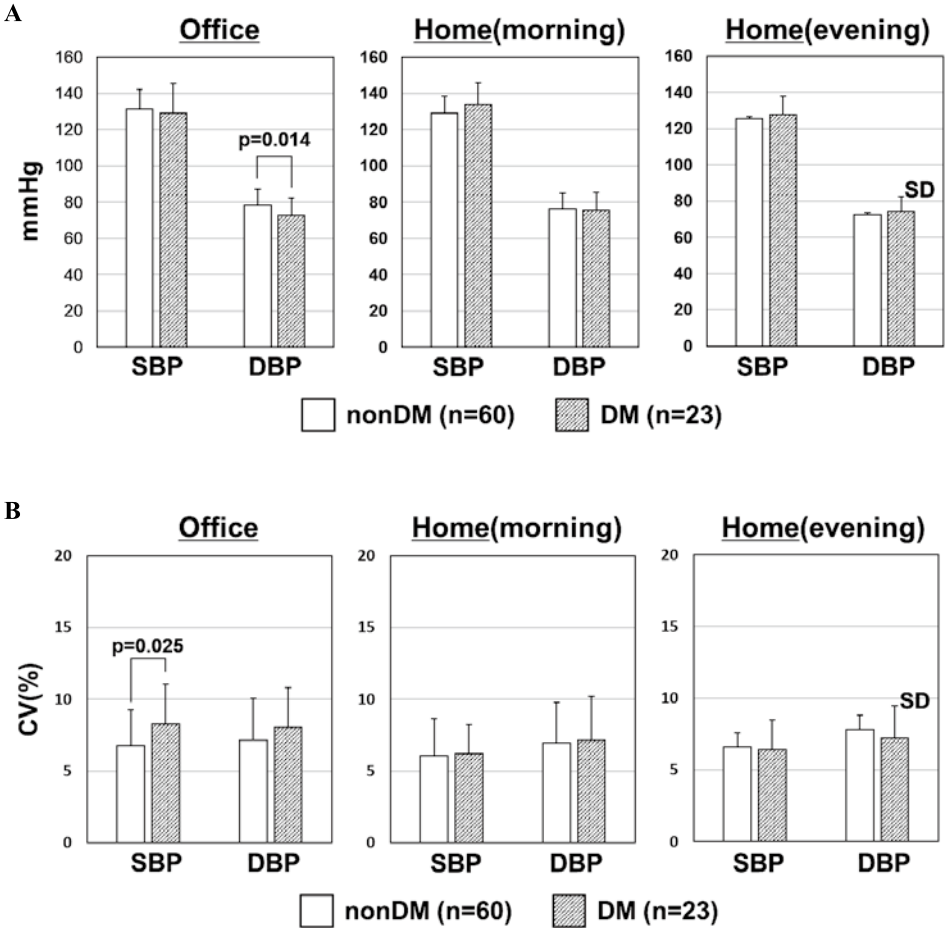

Figure 1

Average values (**A**) and coefficient of variations (**B**) of office and home blood pressures in patients with or without diabetes mellitus (DM). SBP : systolic blood pressure, DBP : diastolic blood pressure.

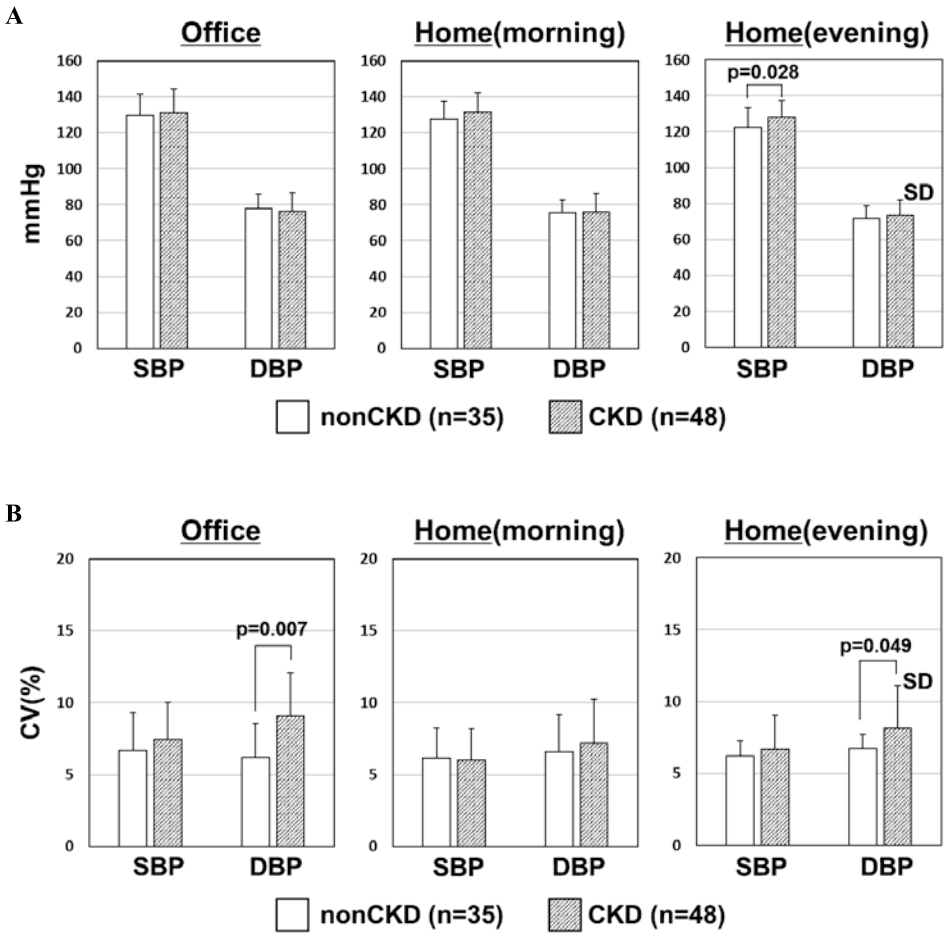

Figure 2

Average values (**A**) and coefficient of variations (**B**) of office and home blood pressures in patients with or without chronic kidney disease (CKD). SBP : systolic blood pressure, DBP : diastolic blood pressure.

between the diabetic and the non-diabetic patients. The CVs of office and home BPs were compared between diabetic and nondiabetic patients in Figure 2B. The CV of office systolic BP was larger in the diabetic patients than that in the nondiabetic patients. On the other hand, the CVs of morning and evening home BPs did not significantly differ between the diabetic and the non diabetic patients.

Figure 2A and 2B displays the office and the home BPs and their CVs in patients with or without CKD. The office BPs were not significantly different between the two groups, however, the evening home systolic BP was higher in the CKD patients than in the nonCKD patients. As for the CV of BP, The CVs of office diastolic BP and evening home diastolic BP were higher in CKD than that in nonCKD.

Office and home BPs and their CVs in patients with CVD were compared in Figure 3A and 3B, respectively. Although the systolic and diastolic office BPs were lower in the CVD patients than in the nonCVD patients, the morning and the evening home BPs were not significantly different between the CVD and the nonCVD patients. On the other hand, the CV of diastolic morning home BP was larger in the CVD patients than that in the nonCVD patients, while the CVs of systolic and diastolic office BPs did not significantly differ between CVD and nonCVD.

Table 7 displays the correlations of office and home BP with the indices of renal function. The morning and evening home systolic BPs showed positive correlations with serum creatinine and a negative correlations with eGFR, while such correlations were not observed between the office BP and renal function (Figure 4). Table 8 displays the correlations of CVs of

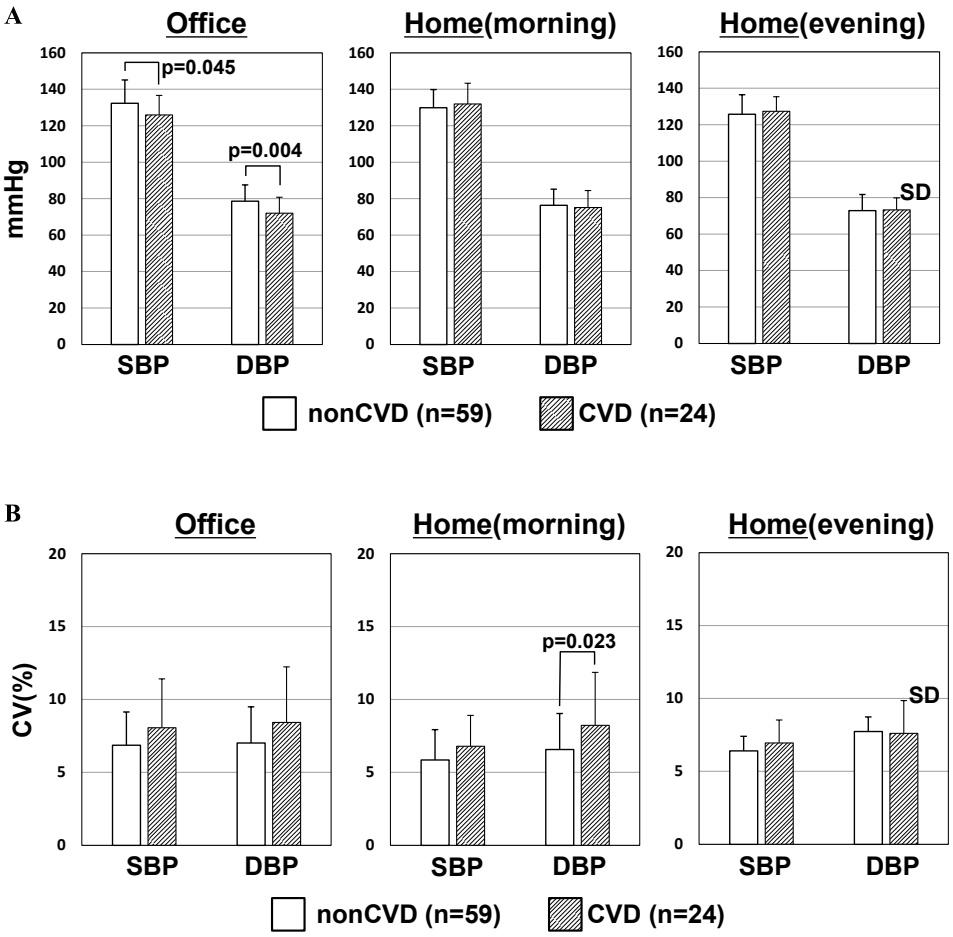

Figure 3

Average values (**A**) and coefficient of variations (**B**) of office and home blood pressures in patients with or without cardiovascular diseases (CVD). SBP : systolic blood pressure, DBP : diastolic blood pressure.

Table 7 Correlations between blood pressure values and indices of renal function

	Serum creatinine		eGFR	
	r	P value	r	P value
Office BP				
Systolic BP	0.201	0.0679	−0.190	0.0847
Diastolic BP	−0.106	0.3403	0.165	0.1362
Morning home BP				
Systolic BP	0.267	0.0155	−0.284	0.0098
Diastolic BP	−0.173	0.1206	0.140	0.2096
Evening home BP				
Systolic BP	0.274	0.0191	−0.297	0.0108
Diastolic BP	−0.181	0.1251	0.109	0.3571

eGFR : estimated glomerular filtration rate, BP : blood pressure, r : correlation coefficient.

Table 8 Correlations between coefficient of variation of blood pressure and indices of renal function

	Serum creatinine		eGFR	
	r	P value	r	P value
Office BP				
Systolic BP	−0.008	0.944	0.004	0.969
Diastolic BP	0.048	0.666	−0.052	0.641
Morning home BP				
Systolic BP	0.174	0.117	−0.058	0.605
Diastolic BP	0.302	0.005	−0.223	0.047
Evening home BP				
Systolic BP	0.210	0.057	−0.134	0.257
Diastolic BP	0.345	0.003	−0.249	0.034

eGFR : estimated glomerular filtration rate, BP : blood pressure, r : correlation coefficient.

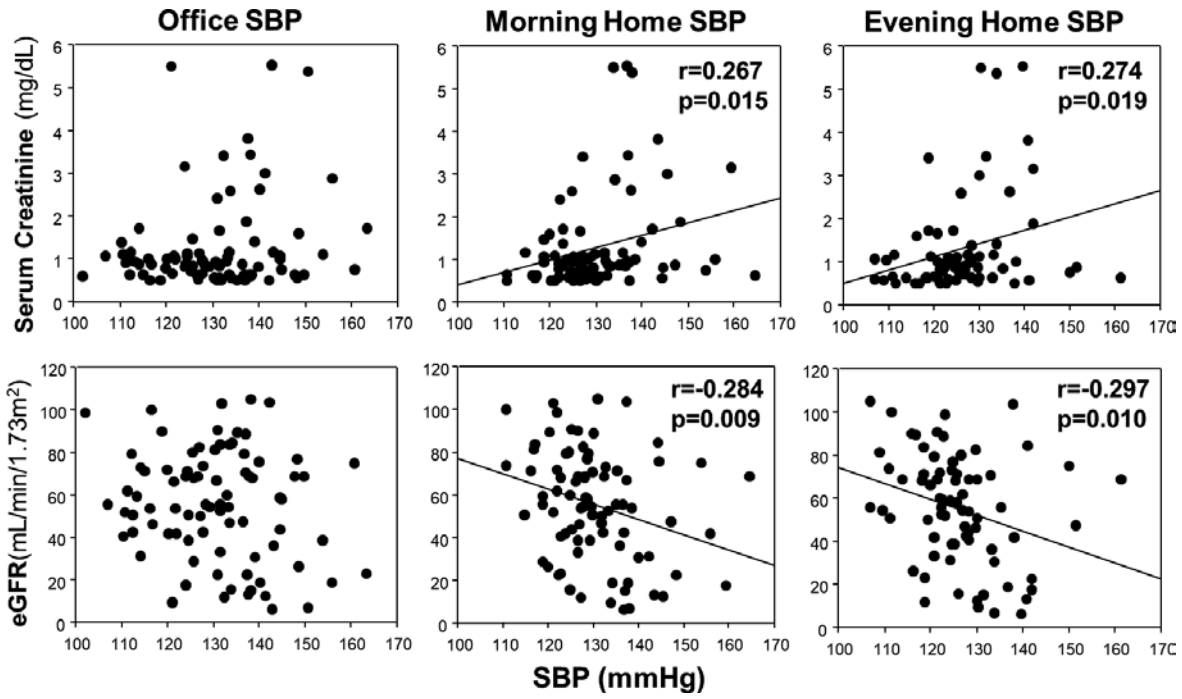

Figure 4

Correlations between average home blood pressure and indices of renal function. SBP : systolic blood pressure, eGFR : estimated glomerular filtration rate.

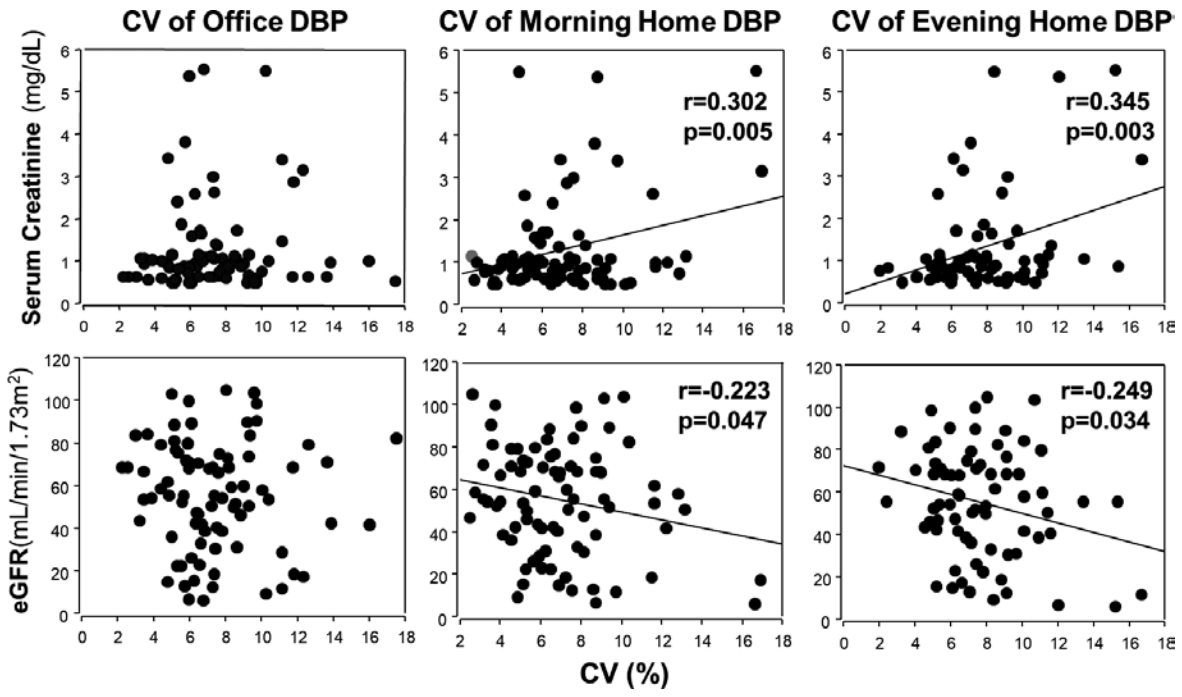

Figure 5

Correlations between average home blood pressure variability and indices of renal function. CV : coefficient of variation, DBP : diastolic blood pressure, eGFR : estimated glomerular filtration rate.

office and home BP with the renal function indices. The CVs of morning and evening home diastolic BP showed positive correlations with serum creatinine and a negative correlations with eGFR, while such correlations were not observed between the CV of office BP and renal function (Figure 5).

DISCUSSION

Large number of hypertensive patients enrolled in this study had cardiovascular risk factors such as diabetes mellitus and dyslipidemia and had complications with CVD and CKD. It is recognized that CKD patients have increased risk of cardiovascular diseases as well as the risk of falling into renal failure requiring renal replacement therapy. Therefore, the large part of patients involved in this study are thought to be at high risk for developing cardiovascular diseases. In high-risk hypertensive patients with diabetes mellitus and or CKD presenting proteinuria, the strict target BP level of less than 130/80 mmHg is recommended[8]. In addition, it is important to control not only the office BP but also the out-of-office BP such as ambulatory BP and home BP in order to prevent cardiovascular disorders sufficiently because, the latter is more intimately associated to the cardiovascular risk. Therefore, it is recommended to take priority in the home BP over the office BP for evaluating and controlling the BP of hypertensive patients[9,10].

BP is an always varying index of cardiovascular hemodynamics. The variability of BP is evaluated in wide range of time phase from seconds to years. The shortest time phase of BP variation is the beat-to-beat BP variation which is subject to the baroreceptor function and the activities of sympathetic and parasympathetic nerve system. This beat-to-beat variation of BP has been shown to correlate with the cardiovascular organ injuries independently of the mean BP level[11,12]. Among the various time phases of BP variation, the diurnal changes have been most widely objective of many studies and a large amount of evidence has been accumulated in implicatings for the risk of developing cardiovascular events and organ injuries. For example, the lack of nocturnal BP decline is defined as nondipper and is known to associate with the increased risk of cardiovascular events and organ injuries[13~17]. The morning surge which is a prominent BP rise in the morning is thought to possibly trigger the cardiovascular events such as stroke[18,19]. In addition, the patients with masked hypertension, which is defined as increased out-of-office BP despite normal office BP, have been shown to likely to develop cardiovascular disorders, while the white-coat hypertension with increased office BP and normal out-of-office BP does not seem to add cardiovascular risk to the patients[20~22].

Much attention has been attracted to the report which showed positive association of visit-to-visit BP variation with the incidence of stroke in patients with transient ischemic attack[4]. The retrospective analysis of ASCOT-BPLA study, in which high-risk hypertensive patients were treated with antihypertensive regimen with a CCB followed by the addition of an ACE inhibitor or a beta blocker followed by the addition of a diuretic, showed that the SD of systolic BP was smaller and the cardiovascular events were fewer in the CCB regimen than that in the beta blocker regimen[23]. On the other hand, the visit-to-visit BP variation was not a significant predictor of cardiovascular events in the post-hoc analysis of Syst-Eur study[24]. Therefore, it seems that the implication of visit-to-visit BP variation as to the risk of cardiovascular disorders still remains a matter of controversy.

In the present study, the CV of office systolic BP was higher in the diabetic patients than that in the non-diabetic patients which may be related to the increased cardiovascular risk loaded by diabetes mellitus. Considering that the dysfunctions of baroreceptor reflex and autonomic nerve system are supposed to increase BP variability, the autonomic nerve impairment due to diabetic neuropathy may have contributed to the exaggeration of BP variation. It has been indicated that the increased visit-to-visit BP variation is related to the renal dysfunction and cardiovascular organ injuries in diabetic patients[25~27].

In addition to the impaired nervous control of BP, the stiffening of arterial wall also augments the variation of BP. The patients with CVD showed greater variation of diastolic morning home BP than the patients without CVD in this study. It is speculated that the development of arteriosclerosis in CVD patients reduces the elasticity of arterial wall and augments the BP changes.

In the patients with CKD, variations of diastolic office BP and diastolic evening home BP were increased in addition to the increase in systolic evening home BP as compared with the patients without CKD. The reduction in renal function has been shown to affect diurnal BP changes and cause non-dipping pattern during night which is corrected by diuretics[28]. The impaired regulation of urinary sodium excretion may increase the body fluid volume and BP changes especially during nighttime. In this context, it seems of interest that the day-to-day variations of morning and evening home BP showed significant correlations with the indices of renal function such as serum creatinine and eGFR. Namely, the home BP variation was increased with the reduction in renal function. It is speculated that the increased blood volume may have contributed to the increase in home systolic BP in CKD patients. On the other hand, the reduction in arterial elasticity may have contributed to the increased diastolic BP variability, because CKD patients are at high risk of developing cardiovascular diseases based on arteriosclerosis[29~32].

As to the effects of antihypertensive drug therapy on the BP variability, the meta-analysis of clinical studies has shown that CCBs have an advantage in reducing BP variation over other classes of antihypertensive drugs[23,33~36]. CCBs directly dilates arterioles and the action is not mediated by intrinsic factors regulating BP such as sodium retention status, sympathetic nerve activity and renin-angiotensin-aldosterone system, while the hypotensive effects of diuretics, β-blockers, ACE inhibitors and ARBs largely depend on these intrinsic factors. Therefore, CCBs are likely to exhibit constant BP reductions irrespective of the status of patients resulting in small BP variations. However, some studies have reported that ARBs have also reduced the visit-to-visit BP variations effectively in hypertensive patients[37] and in patients on renal replacement therapy[38,39]. Considering these, the combination of CCB and ARB seems to be effective in reducing not only the BP level but also the variation of BP. And the addition of diuretic is expected to reduce BP variation derived from sodium retention especially in patients with impaired renal function.

In summary, this study examined the implications of visit-to-visit variation of office BP and day-to-day variation of home BP in hypertensive patients including patients with diabetes mellitus, CKD and or CVD. The visit-to-visit variation of systolic office BP was increased in patients with diabetes mellitus. In CKD patients, visit-to-visit variation of diastolic office BP and day-to-day variation of diastolic evening home BP were increased as compared with non-CKD patients. The patients with CVD showed greater day-to-day variation of diastolic morning home BP than the patients without CVD. Thus, It is indicated that such high-risk hypertensive patients show increased BP variability. In the management of hypertension, it may be desirable to reduce BP variations as well as BP levels in order to achieve effective prevention of cardiovascular diseases and organ injuries.

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