Masked Hypertension Defined by Home Blood Pressure Monitoring Is Associated With Impaired Flow-Mediated Vasodilatation in Patients With Cardiovascular Risk Factors

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The relationships between home blood pressure (BP), masked hypertension defined by home BP, and integrated flow-mediated vasodilation (FMD) response remain unclear. The authors enrolled 257 patients (mean age, 63.5 years; 51% men) who had at least one cardiovascular risk factor. FMD of the brachial artery was measured with a semiautomatic edge-detection algorithm. The integrated FMD response was calculated as the area under the dilation curve during 120 seconds after deflation (FMD-AUC$_{120}$) and the FMD magnitude as the percentage change in peak diameter (ΔFMD). Masked hypertension was defined by office BP <140/90 mm Hg and home BP $\geq$135 mm Hg and/or 85 mm Hg. Home systolic BP was inversely correlated with FMD-AUC$_{120}$ and ΔFMD (FMD-AUC$_{120}$: $r=-.23$, $P<.001$; ΔFMD: $r=-.13$, $P=.041$), and office systolic BP was inversely associated with FMD-AUC$_{120}$ ($r=-.16$, $P=.011$), but not with ΔFMD. After adjusting for covariates, home systolic BP ($\beta=-.27$, $P=.003$), but not office BP, was inversely associated with FMD-AUC$_{120}$, whereas ΔFMD was not associated with office or home systolic BP. FMD-AUC$_{120}$ was significantly lower in patients with masked hypertension compared with those with normotension (7.7$\pm$6.7 vs 11.5$\pm$8.8 mm $\times$ s, $P=.048$). Home systolic BP and masked hypertension defined by home BP were associated with a decrease in FMD-AUC$_{120}$. *J Clin Hypertens (Greenwich).* 2013;15:630–636. ©2013 Wiley Periodicals, Inc.

In recent years, the importance of out-of-office blood pressure (BP) measurement has been widely known,[1–4] and many reports have shown that self-measured home BP could predict cardiovascular (CV) events better than office BP.[5–7] When guided by only office BP, control of BP might be insufficient to prevent CV events.[8] Masked hypertension defined by normal office BP and high *ambulatory* BP has been associated with CV events.[9,10] On the other hand, masked hypertension defined by normal office BP and high *home* BP has also been shown to be associated with an increased risk of CV events,[11–13] hypertensive organ damage, and atherosclerosis.[14,15] Consequently, home BP has been established as the determinant of masked hypertension.[16]

A decrease in flow-mediated vasodilation (FMD) has been shown to predict CV events[17] and hypertensive organ damage.[18] FMD analyses have been widely performed, and a decrease of FMD has been shown to reflect endothelial dysfunction.[19–22] Two studies showed an association between a decrease in FMD and masked hypertension defined by normal office BP and high ambulatory BP.[23,24]

To date, the integrated FMD response has been measured by time-course analysis using continuous measurement in addition to the traditional FMD magnitude, which was calculated as the percentage change in peak diameter from the resting baseline diameter. Although there have also been some reports on the association between CV risk and the integrated FMD response,[25,26] previous reports did not investigate the association between masked hypertension and the integrated FMD response. Thus, the association between masked hypertension defined by home BP and the integrated FMD response remains unclear.

In this study, we hypothesized that home BP and masked hypertension defined by home BP would be associated with integrated FMD response in patients with a CV risk factor.

METHODS

Study Participants
This study was performed as part of the Japan Morning Surge–Home Blood Pressure (J-HOP) study.[27] The protocol of the J-HOP study has been registered at the University Hospital Medical Information Network Clinical Trials Registry Web site under the trial identifier UMIN000000894. Briefly, the J-HOP study is a prospective observational evaluation of predictive values of home BP for CV events in Japanese outpatients with any of the following CV risk factors at the clinic or hospital: hypertension, diabetes mellitus, hyperlipidemia, smokers (including chronic obstructive pulmonary disease), chronic renal disease, atrial fibrillation, metabolic syndrome, and sleep apnea syndrome.

Hypertension was defined by office systolic BP of at least 140 mm Hg, diastolic BP of at least 90 mm Hg, or

both, or as current treatment with antihypertensive medication. Hyperlipidemia was defined by a total cholesterol level >240 mg/dL or by current treatment with an oral lipid-lowering agent. Diabetes mellitus was defined by a fasting glucose level >126 mg/dL, a random nonfasting glucose level >200 mg/dL, or current treatment with an oral hypoglycemic agent or insulin. Smoking was defined by a current smoking habit, as reported previously.[27] A regular drinker was defined as someone who drank alcohol at least 5 days per week.

BP Measurements

Office BP was measured by a nurse using a validated upper-arm cuff oscillometric BP device (HEM-5001; Omron, Kyoto, Japan)[28] with the patient seated after 5 minutes of rest. Three office BP and pulse rate readings were taken at 15-second intervals, and the values of office BP and pulse rate were defined by the average of 6 readings from 2 clinic visits.

Self-measured home BP was also obtained by a validated upper-arm cuff oscillometric device (HEM-5001; Omron, Kyoto, Japan).[28] Home BP was measured on the nondominant upper arm with the patient having remained seated after 2 minutes of rest.[29] The home BP monitoring device automatically took 3 readings at 15-second intervals on each occasion,[30] and the data were stored in the monitor's memory. The rapid method (15-second intervals between BP measurements) was shown to be as accurate as a 1-minute interval.[30] Morning BP was measured within 1 hour after waking, after urination, and before breakfast and the taking of antihypertensive medication. Evening BP was measured immediately before bedtime. Patients were instructed to avoid measuring BP just after taking a bath, drinking alcohol, or smoking. The BP data were downloaded to a computer by the physician or nurses at the time of each clinic visit. Home BP was defined by an average of morning and evening BP during the course of 2 weeks.

We defined normotension by office BP <140/90 mm Hg and home BP <135/85 mm Hg, white-coat hypertension by office BP ≥140 mm Hg and/or 90 mm Hg and home BP<135/85 mm Hg, masked hypertension by office BP <140/90 mm Hg and home BP ≥135 mm Hg and/or 85 mm Hg, and sustained hypertension by office BP ≥140 mm Hg and/or 90 mm Hg and home BP ≥135 mm Hg and/or 85 mm Hg.

Flow-Mediated Vasodilation

The details of FMD measurement have been published elsewhere.[26] Participants were examined after 15 minutes of rest in the fasting state (ie, after 12-hour fasting and not taking any medications), and patients were instructed to avoid exercise for at least 4 to 6 hours prior to the FMD examination.[21] The brachial artery was imaged using an instrument equipped with software for monitoring the brachial artery diameter. This system was equipped with a 10-MHz linear array transducer and a novel stereotactic probe-holding device (UNEX EF 18G; Unex Co, Ltd, Nagoya, Japan).[31] After baseline

images of the brachial artery were recorded, occlusion of the forearm blood flow was initiated and maintained for a period of 5 minutes by a cuff inflated to 50 mm Hg above the participant's systolic BP. Images of the brachial artery were recorded for a 2-minute duration after cuff deflation.[21] All FMD measurements were obtained by a physician (TK) blinded to the clinical data.

FMD Time Course Analysis

As reported previously,[26] the FMD magnitude (ΔFMD) was calculated as the percentage change in peak diameter from the resting baseline diameter, and the integrated FMD response (FMD-AUC_{120}) was calculated as the area under the dilation curve during the 120-second dilation period after cuff deflation (Figure 1). In addition, we investigated the FMD magnitude in the percentage change at 90 seconds and 120 seconds from the resting baseline diameter (FMD at 90 seconds and 120 seconds) to examine the dilation reaction after its peak.

Blood Samples

Blood samples were drawn from the antecubital vein in a fasting state at the second clinic visit. We measured the levels of total cholesterol, triglycerides, fasting glucose, and hemoglobin A_{1c} (HbA_{1c}). All blood samples were measured at a single laboratory (SRL Inc, Tokyo, Japan).

Statistical Analysis

Data are shown as the mean±standard deviation or as a percentage. The distribution of all variables was examined using the Kolmogorov-Smirnov test of normality. To approximate normal distribution, natural log-transformed values for triglycerides, fasting glucose, and HbA_{1c} were used in the analysis. The associations among the continuous clinical parameters, FMD-AUC_{120} and ΔFMD, were assessed using Pearson's correlation coefficient. The χ^2 test was used for categoric data. Unpaired *t* tests were used for normally distributed data and for comparisons between two
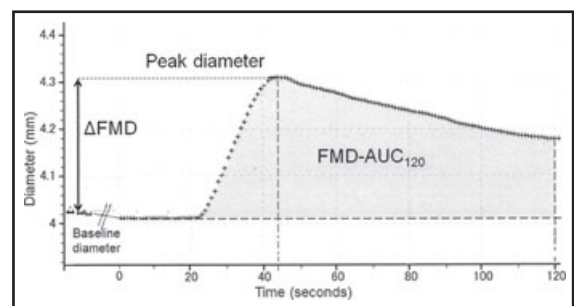

FIGURE 1. Time course analysis of flow-mediated vasodilation (FMD). ΔFMD, FMD magnitude in percentage change in peak diameter from baseline; FMD-AUC_{120}, integrated FMD response calculated as the area under the dilation curve during the 120-second dilation period after cuff deflation.

groups, and analysis of variance was used for comparisons of more than two groups. The results of multiple linear regression analysis to assess the independent associations between office BP, home systolic BP, and FMD-AUC$_{120}$ and ΔFMD were adjusted for age and sex. Variables with $P<.05$ in univariate analysis were included in the model. The office systolic BP and home systolic BP were included together in the same model because of the low degree of multicollinearity (the variance inflation factor was 1.65 to 1.70 when both variables were included in the same model). Bonferroni's analysis was used for comparisons of FMD-AUC$_{120}$ and ΔFMD among subgroups defined by office and home BP. The differences in FMD-AUC$_{120}$ and ΔFMD in masked hypertension and normotension were assessed by analysis of covariance with adjustment for age, sex, diabetes, hyperlipidemia, smoking status, and HbA$_{1c}$, followed by the Bonferroni post hoc test. Computer software (SPSS version 16.0; SPSS Inc, Chicago, IL) was used for the analyses. A probability value $<.05$ was considered statistically significant.

RESULTS

The clinical characteristics of the patients are shown in Table I. The average age was 63.5 ± 11.4 years and 51% of participants were men.

TABLE I. Patient Characteristics

Parameter	Value
Patients, No.	257
Age, y	63.5±11.4
Men, %	51
Body mass index, kg/m^2	24.4±3.7
Current smoker, %	11
Regular drinker, %	20
Hyperlipidemia, %	33
Diabetes mellitus, %	23
Antihypertensive therapy, %	76
Antihypertensive medication, No.	1.6±1.3
Office systolic blood pressure, mm Hg	138±16
Office diastolic blood pressure, mm Hg	80±12
Office pulse rate, beats per min	72±12
Home systolic blood pressure, mm Hg	135±16
Home diastolic blood pressure, mm Hg	77±12
Home pulse rate, beats per min	67±9
Total cholesterol, mg/dL	201±33
Triglyceride, mg/dL	130±84
Fasting glucose, mg/dL	110±27
Hemoglobin A$_{1c}$, %	5.5±.8
Brachial artery parameters	
FMD-AUC$_{120}$, mm × s	9.4±7.4
ΔFMD, %	5.1±4.6

Values are expressed as mean±standard deviation or percentage of patients. Abbreviations: ΔFMD, flow-mediated vasodilation (FMD) magnitude in percentage change in peak diameter from baseline; FMD-AUC$_{120}$, integrated FMD response calculated as the area under the dilation curve during the 120-second dilation period after cuff deflation.

FMD-AUC$_{120}$ and ΔFMD values were similar between men and women, smokers and nonsmokers, drinkers and nondrinkers, and patients with and without hyperlipidemia, diabetes, antihypertensive medication use, and statin use (Table II). We analyzed BP levels between patients who were taking antihypertensive medication and those who were not. Office systolic/diastolic BP was $138\pm16/83\pm13$ mm Hg in patients taking antihypertensive medication (n=61) and $138\pm16/80\pm12$ mm Hg in patients not taking antihypertensive medication (n=196). Home systolic/diastolic BP was $134\pm16/77\pm12$ mm Hg in patients taking antihypertensive medication and $136\pm15/76\pm11$ mm Hg in patients not taking antihypertensive medication. The differences in office and home systolic/diastolic BPs between the two groups were not significant.

BP and FMD-AUC$_{120}$

Home systolic BP and office systolic BP were significantly inversely correlated with FMD-AUC$_{120}$ (home systolic BP: $r=-.23$, $P<.001$; office systolic BP: $r=-.16$, $P=.011$; Table III). Home systolic BP was associated with ΔFMD, but office systolic BP was not associated with ΔFMD (Table III). Office or home diastolic BP or pulse rate was not associated with FMD-AUC$_{120}$ or with ΔFMD (Table III).

Multivariate logistic regression analysis including age, sex, antihypertensive medication, and both office and home systolic BP revealed that home systolic BP was independently associated with FMD-AUC$_{120}$ ($\beta=-.27$, $P=.003$), but was not independently associated with ΔFMD (Table III).

Masked Hypertension and FMD-AUC$_{120}$

Table IV shows patient characteristics for comparison among subgroups of office and home BP.

Adjusting for age, sex, diabetes, hyperlipidemia, smoking status, and HbA$_{1c}$, FMD-AUC$_{120}$ was significantly lower in patients with masked hypertension than in those with normotension (7.7 ± 6.7 vs 11.5 ± 8.8 mm × s, $P=.048$; Figure 2, Panel A). Meanwhile, ΔFMD in patients with masked hypertension did not significantly differ from that in patients with normotension ($4.5\%\pm4.2\%$ vs $5.7\%\pm4.8\%$, $P=1.00$; Figure 2, Panel B).

We showed two typical cases (Figure 3, Panels A and B). Panel A shows high FMD-AUC$_{120}$ and ΔFMD in a patient with normotension, and panel B shows reduced FMD-AUC$_{120}$ and ΔFMD in a patient with masked hypertension.

Dilation Reaction After Its Peak and the Time in Seconds Needed to Achieve Peak Diameter After Cuff Release

Office and home systolic BP were significantly associated with FMD at 90 seconds (office systolic BP: $r=-.14$, $P=.025$; home systolic BP: $r=-.20$, $P=.001$), and home systolic BP, but not office systolic BP, was

TABLE II. Clinical Patient Characteristics and FMD Parameters

Covariates	FMD AUC$_{120}$, mm × s	P Value	ΔFMD, %	P Value
Sex				
Male (n=131)	9.3±6.9	.799	4.9±4.1	.435
Female (n=126)	9.5±8.0		5.3±5.1	
Current smoker				
Yes (n=29)	11.0±7.2	.205	5.5±3.8	.536
No (n=228)	9.2±7.5		4.9±4.6	
Regular drinker				
Yes (n=52)	11.0±6.7	.085	4.7±4.1	.388
No (n=205)	9.0±7.6		5.2±4.8	
Hyperlipidemia				
Present (n=85)	10.2±8.9	.229	5.6±4.4	.097
Absent (n=172)	9.0±6.6		4.7±4.7	
Diabetes mellitus				
Present (n=58)	10.1±8.7	.413	5.6±4.1	.327
Absent (n=199)	9.2±7.0		4.9±4.7	
Antihypertensive medication				
Present (n=196)	9.0±6.9	.131	4.9±4.2	.179
Absent (n=61)	10.7±8.8		5.8±5.7	
Statin use				
Present (n=64)	10.2±8.9	.323	5.5±4.1	.414
Absent (n=193)	9.1±6.9		5.0±4.8	

Values are expressed as mean±standard deviation or percentage of patients. Abbreviations: ΔFMD, flow-mediated vasodilation (FMD) magnitude in percentage change in peak diameter from baseline; FMD-AUC$_{120}$, integrated FMD response calculated as the area under the dilation curve during the 120-second dilation period after cuff deflation.

TABLE III. Univariate and Multivariate Regression Analysis of FMD-AUC$_{120}$ and ΔFMD

	FMD-AUC$_{120}$				ΔFMD			
	Univariate		Multivariate		Univariate		Multivariate	
Covariate	r	P Value	β	P Value	r	P Value	β	P Value
Age	−.20	.001	−.17	.014	−.09	.132	−.06	.435
Body mass index	−.03	.640	–	–	−.08	.182	–	–
Office systolic blood pressure	−.16	.011	.01	.921	−.07	.249	−.04	.664
Office diastolic blood pressure	−.02	.570	–	–	.02	.725	–	–
Office pulse rate	−.02	.805	–	–	.02	.793	–	–
Home systolic blood pressure	−.23	<.001	−.27	.003	−.13	.041	−.06	.513
Home diastolic blood pressure	−.06	.350	–	–	−.02	.780	–	–
Home pulse rate	−.02	.802	–	–	−.01	.906	–	–
Total cholesterol	.07	.282	–	–	.02	.721	–	–
Log triglyceride	−.05	.432	–	–	−.02	.703	–	–
Log fasting glucose	−.08	.184	–	–	.00	.984	–	–
Log hemoglobin A$_{1c}$	.00	.999	–	–	.05	.427	–	–

Multiple linear regression analysis was performed to determine the variables with independent significant association with flow-mediated vasodilation (FMD) response calculated as the area under the dilation curve during 120 seconds after deflation (FMD-AUC$_{120}$). Age, sex, office and home systolic blood pressure, and variables with P<.05 in univariate analysis were included in the model (calcium channel blocker use).

associated with FMD at 120 seconds (home systolic BP: $r=-.18$, $P=.004$; office systolic BP: $r=-.11$, $P=.08$).

DISCUSSION

The major findings of the present study were (1) home systolic BP was associated with FMD-AUC$_{120}$ (a new measure of FMD) independently of office systolic BP, and (2) masked hypertension defined by normal office BP and high home BP was significantly associated with FMD-AUC$_{120}$ in patients with CV risk.

To the best of our knowledge, there are no data on the association between home systolic BP, masked hypertension defined by home BP, and a decrease in FMD. In this study, home systolic BP, but not office BP, was associated with a decrease in FMD-AUC$_{120}$. It has been shown that left ventricular mass and carotid wall

TABLE IV. Comparison of Subgroups Defined by Office and Home Blood Pressure

Covariate	Normotension (n=90)	White-Coat Hypertension (n=41)	Masked Hypertension (n=41)	Sustained Hypertension (n=85)	P Value
Age, y	63.7±10.2	63.9±12.6	65.3±9.6	62.4±12.9	.606
Men, %	47	59	44	55	.386
Body mass index, kg/m^2	23.9±3.2	24.3±3.4	24.8±3.6	24.9±3.4	.238
Current smoker, %	6.7	9.8	15	15	.282
Regular drinker, %	17	27	24	19	.505
Antihypertensive medication, %	73	71	80	76	.793
Hyperlipidemia, %	46	17[a]	32	27	.006
Diabetes mellitus, %	26	12	34	19	.078
Office systolic blood pressure, mm Hg	124±10	147±6[b]	130±7[b,c]	152±12[b,d]	<.001
Office diastolic blood pressure, mm Hg	74±8	83±8[b]	75±9[e]	88±13[b,d]	<.001
Office pulse rate, beats per min	72±10	74±13	69±13	74±13	.211
Home systolic blood pressure, mm Hg	122±9	128±6[f]	144±9[b,c]	148±14[b,c]	<.001
Home diastolic blood pressure, mm Hg	71±8	72±7	79±11[b,g]	84±13[b,c]	<.001
Home pulse rate, beats per min	66±9	67±9	67±10	69±10	.467
Total cholesterol, mg/dL	196±33	202±31	198±33	208±32	.100
Triglycerides, mg/dL	130±86	117±75	131±69	137±91	.667
Fasting glucose, mg/dL	108±26	107±14	116±31	109±31	.318
Hemoglobin A$_{1c}$, %	5.5±.8	5.3±.6	5.9±1.0[e,f]	5.5±.8	.007

[a]P<.01. [b]P<.001 vs normotension. [c]P<.001 vs white-coat hypertension. [d]P<.001 vs masked hypertension. [e]P<.01 vs. white-coat hypertension. [f]P<.05 vs. normotension. [g]P<.05 vs. white-coat hypertension by Bonferroni's analysis. [Correction added after online publication 25-Jun-2013: The P value information has been updated.]
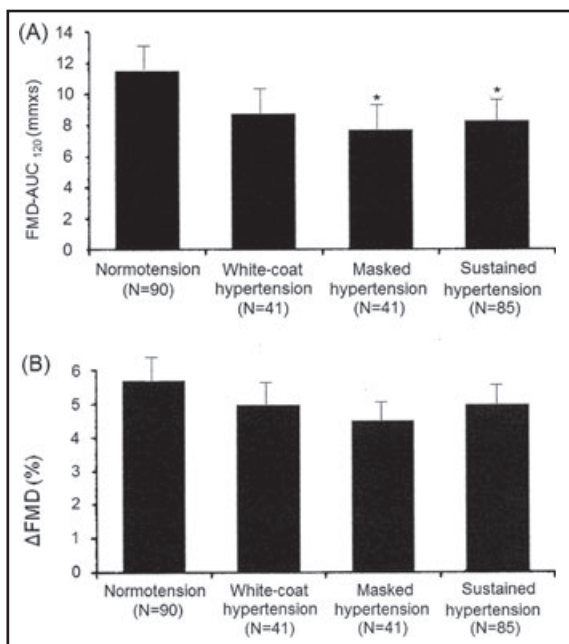

FIGURE 2. Integrated flow-mediated vasodilation (FMD) response calculated as the area under the dilation curve during the 120-second dilation period after cuff deflation (FMD-AUC$_{120}$) and FMD magnitude in percentage change in peak diameter from baseline (ΔFMD) in patients with normotension, white-coat hypertension, masked hypertension, and sustained hypertension. *P<.05 vs normotension by Bonferroni's analysis.
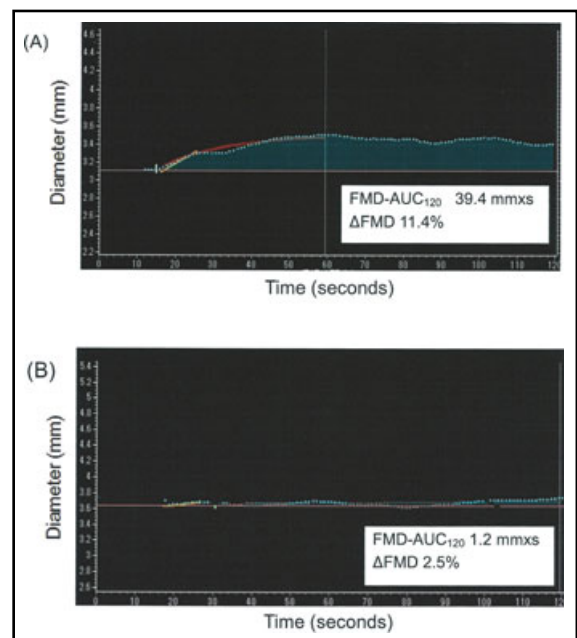

FIGURE 3. Two cases of real-time semiautomatic analysis of integrated flow-mediated vasodilation (FMD) response calculated as the area under the dilation curve during the 120-second dilation period after cuff deflation (FMD-AUC$_{120}$). (A) A 52-year-old woman. Office blood pressure 122/72 mm Hg, home blood pressure 101/59 mm Hg, hyperlipidemia (+), diabetes mellitus (−), nonsmoker. (B) A 66-year-old woman. Office blood pressure 122/68 mm Hg, home blood pressure 167/81 mm Hg, hyperlipidemia (+), diabetes mellitus (+), nonsmoker. ΔFMD indicates FMD magnitude in percentage change in peak diameter from baseline.

thickening are associated with a decrease in FMD.[32,33] Left ventricular hypertrophy and carotid wall thickening have been associated with home BP in earlier studies,[14,34,35] and the significant association between home BP and FMD-AUC$_{120}$ observed in this study is consistent with the findings in these previous reports. Endothelial dysfunction evaluated by FMD is a manifestation of the early stage of atherosclerosis,[36] and might precede left ventricular hypertrophy and carotid wall thickening. There have been few papers on the use of antihypertensive therapy to reduce home BP and hypertensive organ damage.[37] Further studies will be needed to investigate the usefulness of FMD-AUC$_{120}$ as a marker of hypertensive organ damage, and whether FMD-AUC$_{120}$ can be increased by a reduction in home BP.

Home systolic BP was significantly associated with FMD-AUC$_{120}$ after adjustment for covariates. Both home systolic BP and masked hypertension were significantly associated with FMD-AUC$_{120}$, but not with ΔFMD. This might be because FMD-AUC$_{120}$ was an integral value that included the dilation reaction after its peak. The time in seconds needed to achieve peak diameter was 71±25 seconds, and home systolic BP was associated with FMD at 90 and 120 seconds. The dilation reaction after its peak might be associated with CV risk factors,[25] and further studies will be needed to clarify the association between CV risk factors and the dilation reaction after its peak.

In this study, masked hypertension defined by normal office BP and high home BP was significantly associated with a decrease in FMD-AUC$_{120}$. Masked hypertension defined by normal office BP and high home BP has been shown to be associated with an increased risk of CV events,[11–13] hypertensive organ damage, and atherosclerosis.[14,15] The association between decreased FMD and masked hypertension defined by normal office BP and high home BP is also consistent with the findings of these previous reports. Although those studies showed an association between decreased FMD and masked hypertension defined by normal office BP and high *ambulatory* BP,[23,24] there is no evidence of an association between a decrease in FMD and masked hypertension defined by normal office BP and high *home* BP.

As reported previously,[26] FMD-AUC$_{120}$ was associated with CV risk in patients at risk for experiencing CV events. In addition, it was established that ΔFMD is useful for predicting the prognosis in patients at low CV risk, but it might not be as useful in patients at high CV risk[38] or in patients 50 years or older.[30] In this study, we enrolled relatively older and higher-risk patients. Instead of the traditional FMD magnitude, FMD-AUC$_{120}$ might be a useful marker of hypertensive organ damage in patients with a CV risk factor. We have already shown a positive association between the CV risk score and FMD-AUC$_{120}$[26]. Further studies will be needed to clarify the association between FMD-AUC$_{120}$, CV risk factors, and subsequent CV events.

Limitations

This study has some limitations. First, the associations between FMD-AUC$_{120}$ and risk factors (hyperlipidemia and diabetes mellitus) other than hypertension were not significant in this study. We recruited patients with CV risk; in particular, most of them were hypertensive. The reason why BP strongly affected FMD-AUC$_{120}$ might be the high prevalence of hypertension, and the contribution of CV risk factors other than hypertension (hyperlipidemia and diabetes mellitus) might become weak. Population-based studies including patients of different ethnic groups will be needed. Secondly, this study was cross-sectional,[26] and the causal relationship was unclear. Finally, we did not measure nitroglycerine-mediated dilation and therefore could not compare FMD and nitric oxide–independent vasodilation.

CONCLUSIONS

Home systolic BP was associated with a decrease in FMD-AUC$_{120}$. In particular, FMD-AUC$_{120}$ was significantly lower in patients with masked hypertension defined by home BP than in those with normotension. FMD-AUC$_{120}$ well reflected home systolic BP rather than office systolic BP.

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