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ORIGINAL ARTICLE

Could home arterial stiffness index be a novel marker for arterial stiffness in patients with type 2 diabetes?

Michiaki Fukui[1], Emi Ushigome[1], Muhei Tanaka[1], Masahide Hamaguchi[2], Toru Tanaka[3], Haruhiko Atsuta[4], Masayoshi Ohnishi[5], Yohei Oda[6], Goji Hasegawa[1] and Naoto Nakamura[1]

Recent studies suggested that home arterial stiffness index (HASI) may be a new measure of arterial stiffness. The aim of this study was to investigate whether HASI is more strongly associated with arterial stiffness than is pulse pressure (PP) and thus a more suitable tool than PP for evaluating arterial stiffness in patients with type 2 diabetes. We evaluated the relationship of HASI or PP with pulse wave velocity (PWV) as well as with major cardiovascular risk factors in 332 patients with type 2 diabetes. Furthermore, we compared the area under the receiver-operator characteristic curve (AUC) of HASI or PP for PWV. Morning PP was positively associated with PWV ($r = 0.303$, $P < 0.0001$), while morning HASI was not ($r = -0.006$, $P = 0.9063$). Multiple regression analysis demonstrated that morning PP ($\beta = 0.179$, $P = 0.0210$), but not morning HASI ($\beta = -0.040$, $P = 0.5036$), was independently associated with PWV. The AUCs (95% confidence interval (CI)) of morning HASI and morning PP for arterial stiffness were 0.510 (0.448–0.573) ($P = 0.745$) and 0.638 (0.578–0.698) ($P < 0.0001$), respectively. The AUC (95% CI) of morning HASI for arterial stiffness was significantly less than that of morning PP ($P = 0.0005$). In conclusion, morning HASI is less correlated with PWV than is morning PP in patients with type 2 diabetes.
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INTRODUCTION

Recently, the ambulatory arterial stiffness index (AASI), which is derived from the linear relationship between 24-h ambulatory systolic and diastolic blood pressure measurements, has been proposed as an easy measure of arterial stiffness.[1] Furthermore, previous studies have demonstrated that AASI is associated with target organ damage, such as stroke and cardiovascular disease.[2] Although AASI has been validated, ambulatory blood pressure monitoring is uncommonly used in routine clinical practice. Home blood pressure has been found to have a stronger relationship with target organ damage than clinic blood pressure in several population-based studies and prospective clinical studies.[3,4] As home blood pressure monitoring is less costly, more widely available and better accepted by patients than ambulatory blood pressure monitoring, the application of the home arterial stiffness index (HASI) would have considerable potential for wide use in clinical practice if HASI could be a useful marker for arterial stiffness.

Qureshi et al.[5] have demonstrated that HASI is significantly correlated with pulse wave velocity (PWV) and left ventricular mass index. Xu et al.[6] reported that the AASI, but not the HASI, is associated with PWV. Thus, HASI has prompted considerable controversy and debate as to whether it is a true measure of arterial stiffness.

Pulse pressure (PP) increases concomitantly with arterial stiffness because the stiffer the aorta is, the faster the reflected pressure wave returns to the heart and superimposes in the forward wave during late systole.[7] PP has been reported to be linked to micro- and macrovascular complications and arterial stiffness.[8]

Arterial stiffness can be assessed simply, noninvasively and reproducibly by measuring PWV along the thoracoabdominal aorta.[9] PWV is a marker for both severity of vascular damage and prognosis in atherosclerotic vascular disease.[10] However, the classic methods to evaluate arterial stiffness require special expensive equipment and trained observer.

There has been no study investigating the association between HASI and arterial stiffness in patients with type 2 diabetes. We hypothesized that if HASI were a useful marker for arterial stiffness, it would have considerable potential for wide use in clinical practice. The aim of this study was to investigate whether HASI is more strongly associated with arterial stiffness evaluated by PWV and thus would be a more suitable tool than PP for evaluating arterial stiffness in patients with type 2 diabetes.

[1]Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan; [2]Immunology Frontier Research Center, Osaka University, Osaka, Japan; [3]Department of Diabetes, Endocrinology and Reumatology, Kyoto First Red Cross Hospital, Kyoto, Japan; [4]Department of Metabolism, Endocrinology and Nephrology, Kyoto Second Red Cross Hospital, Kyoto, Japan; [5]Department of Diabetes and Metabolism, Osaka General Hospital of West Japan Railway Company, Osaka, Japan and [6]Department of Cardiology, Social insurance Kyoto Hospital, Kyoto, Japan
Correspondence: Dr M Fukui, Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
E-mail: sayarinapm@hotmail.com
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METHODS

Patients

Home blood pressure measurements were performed in patients with type 2 diabetes who had regularly attended the diabetes outpatient clinic at the Hospital of Kyoto Prefectural University of Medicine, Kyoto, Japan and the other four general hospitals as previously reported.[11] A total of 954 type 2 diabetic patients agreed to participate in the present study. First, 31 patients who conducted home blood pressure measurement for <4 consecutive days[12] were excluded. We randomly measured PWV and 567 patients, whose PWV data were not available, were also excluded. In addition, 10 patients who had advanced renal dysfunction (serum creatinine $\geqslant 2.0\,\mathrm{mg\,dl}^{-1}$) and 14 patients whose ankle-brachial index <0.95[13] were excluded from the analyses. Finally, 332 patients comprised the study population (175 male, 157 female). Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[14] Retinopathy was assessed with a state of mydriasis by ophthalmologists who were unaware of the data, and was graded as follows: no diabetic retinopathy; simple diabetic retinopathy; and proliferative, including preproliferative, diabetic retinopathy. If the finding in the left and right fundi were discordant, the worse side was taken as a representative for the subject. Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion $<30\,\mathrm{mg}$ per gram of creatinine $(\mathrm{mg\,g}^{-1}\,\mathrm{Cr})$; microalbuminuria, $30\text{--}300\,\mathrm{mg\,g}^{-1}\,\mathrm{Cr}$; or macroalbuminuria, $>300\,\mathrm{mg\,g}^{-1}\,\mathrm{Cr}$. Neuropathy was defined by the diagnostic criteria for diabetic neuropathy proposed by the Diagnostic Neuropathy Study Group.[15] In brief, in the absence of peripheral neuropathies, diabetic neuropathy is diagnosed by $\geqslant 2$ of the following: neuropathic symptoms such as numbness, paresthesia and neuropathic pain, decreased or absent ankle reflex (bilateral), and decreased distal sensation. Cardiovascular disease was defined as a previous myocardial or cerebral infarction based on the clinical history or physical examination. Subjects were classified as nonsmokers, past smokers or current smokers according to a self-administered questionnaire.

Study design

We designed a cross-sectional multicenter study in general hospitals, which are located in Kansai area in Japan. First, we evaluated relationships of HASI or PP to PWV as well as to major cardiovascular risk factors, including age, serum lipid concentration and hemoglobin A1c, using a linear regression analysis. Second, we performed multiple regression analysis to determine the contribution of the variables on PWV. Finally, we compared area under the receiver-operator characteristic curve (AUC) of HASI or PP for arterial stiffness defined as PWV $\geqslant 1800\,\mathrm{cm\,s}^{-1}$. This study was approved by the local Research Ethics Committee and was conducted in accordance with Declaration of Helsinki, and informed consent was obtained from all the participants.

Data collection

Blood samples for biochemical measurements were taken at the hospital. Serum total cholesterol, triglycerides and high-density lipoprotein cholesterol concentrations were assessed using standard enzymatic methods. HemoglobinA1c was assayed using high-performance liquid chromatography with the standard provided by the National Glycohemoglobin Standardization Program. Urinary albumin excretion was measured with an immunoturbidimetric assay. A mean value for urinary albumin excretion was determined from three urine collections. Home blood pressure measurements were self-measured using an automatic memory-equipped device, (HEM-70801C; Omron Healthcare, Kyoto, Japan), which uses the cuff-oscillometric method to generate a digital display of heart rate and systolic/diastolic blood pressure value. HEM-70801C uses the identical components and blood pressure determining algorithm to those of another device, HEM-705IT, which was previously validated and satisfied the criteria of the British Hypertension Society protocol.[16] Patients received written instructions and individual guidance on how to self-measure triplicate morning and evening home blood pressure measurements for 14 consecutive days. Measurements of morning home blood pressure were made within 1 h of waking, before breakfast or taking any drugs, with the patient seated and rested for at least 5 min.[17] Measurements of evening home blood pressure were obtained in a homologous way just before going to bed.

Measurement of PVW

Brachial-ankle PWV was measured using a Colin Waveform Analyzer (form PWV/ankle-brachial index/toe brachial index; Colin Medical Technology, Komaki, Japan), which simultaneously measures pulse volumes in the brachial and posterior tibial or toe arteries using an oscillometric method together with bilateral arm and ankle or toe blood pressure. PWV was measured after allowing the patient to rest in the supine position for at least 5 min. Details of the method have been described elsewhere.[18] After bilateral determination of brachial-ankle PWV, the higher value was taken as a representative for each subject.

HASI estimation

The regression slope of diastolic on systolic blood pressure was computed for each individual on the basis of home blood pressure readings. HASI was defined as one minus the respective regression slope.[1]

Statistical analysis

Means and frequencies of potential confounding variables were calculated. The relationships between HASI or PP and PWV, age, glycemic control or other variables were examined by Pearson's correlation analyses, using Stat View software (version 5.0; SAS Institute, Cary, NC, USA). In multiple regression analysis to assess the effects of variables on PWV, we included the following independent variables: age, gender, duration of diabetes, body mass index, mean arterial pressure, hemoglobin A1c, total cholesterol, triglycerides, smoking, alcohol and HASI or PP. Receiver-operator characteristic analyses were performed to calculate AUC of HASI or PP for arterial stiffness defined as PWV $\geqslant 1800\,\mathrm{cm\,s}^{-1}$, using the ROCKIT (http://xray.bsd.uchicago.edu/krl/roc_soft.htm). All continuous variables are presented as the mean ± s.d. A P value <0.05 was considered statistically significant.

RESULTS

The clinical characteristics of patients with type 2 diabetes are shown in Table 1. The average number of morning and evening home systolic blood pressure measurements per patient during the 14-day study period was 39.3 ± 6.4 and 37.3 ± 8.0, respectively. The relationships between HASI or PP and the characteristics of patients with type 2 diabetes are shown in Table 2. Age was positively associated with morning HASI, and age, duration of diabetes and PWV were positively associated with morning PP. Duration of diabetes and PWV were positively associated with evening HASI, and age, duration of diabetes and PWV were positively associated with evening PP. Age $(r=0.141, P=0.0113)$ and PWV $(r=0.113, P=0.0404)$ were positively associated with HASI in the morning and evening, and age $(r=0.351, P<0.0001)$, duration of diabetes $(r=0.216, P<0.0001)$ and PWV $(r=0.319, P<0.0001)$ were positively associated with PP in the morning and evening. Morning HASI correlated significantly with morning PP $(r=0.271, P<0.0001)$, and evening HASI correlated significantly with evening PP $(r=0.289, P<0.0001)$. HASI in the morning and evening correlated significantly with PP in the morning and evening $(r=0.314, P<0.0001)$. Multiple regression analysis demonstrated that age $(\beta=0.216, P=0.0012)$, gender $(\beta=-0.169, P=0.0245)$ and mean arterial pressure $(\beta=0.209, P=0.0012)$, but not morning HASI $(\beta=-0.040, P=0.5036)$, were independently associated with PWV, and age $(\beta=0.154, P=0.0273)$ and morning PP $(\beta=0.179, P=0.0210)$ were independently associated with PWV (Table 3). Age $(\beta=0.219, P=0.0008)$, body mass index $(\beta=-0.130, P=0.0382)$, alcohol $(\beta=0.160, P=0.0137)$, mean arterial pressure $(\beta=0.208, P=0.0007)$ and evening HASI $(\beta=0.166, P=0.0058)$ were independently associated with PWV, and age $(\beta=0.178, P=0.0094)$, alcohol $(\beta=0.152, P=0.0188)$ and evening PP $(\beta=0.182, P=0.0114)$ were independently associated with PWV (Table 3). Age $(\beta=0.213, P=0.0012)$, alcohol $(\beta=0.132, P=0.0434)$ and mean arterial pressure $(\beta=0.228, P=0.0002)$, but

not HASI in the morning and evening ($\beta = 0.085$, $P = 0.1573$), were independently associated with PWV, and age ($\beta = 0.165$, $P = 0.0166$), alcohol ($\beta = 0.131$, $P = 0.0431$), mean arterial pressure ($\beta = 0.151$, $P = 0.0309$) and PP in the morning and evening ($\beta = 0.183$, $P = 0.0131$) were independently associated with PWV. AUC (95% confidence interval (CI)) of morning HASI and morning PP for arterial stiffness were 0.510 (0.448–0.573) ($P = 0.745$) and 0.638 (0.578–0.698) ($P < 0.0001$), respectively. AUC (95% CI) of morning

HASI for arterial stiffness was significantly less than that of morning PP ($P = 0.0005$; Figure 1a). AUC (95% CI) of evening HASI and evening PP for arterial stiffness were 0.600 (0.539–0.661) ($P = 0.002$) and 0.638 (0.578–0.698) ($P < 0.0001$), respectively. AUC (95% CI) of evening HASI for arterial stiffness did not differ from that of evening PP ($P = 0.0757$; Figure 1b). The AUCs (95% CI) of HASI in the morning and evening and of PP in the morning and evening for arterial stiffness were 0.568 (0.506–0.629) ($P = 0.033$) and 0.643 (0.583–0.703) ($P < 0.0001$), respectively. The AUC (95% CI) of HASI in the morning and evening for arterial stiffness was significantly less than that of PP in the morning and evening ($P = 0.0397$).

DISCUSSION

The present study demonstrated that the AUC of morning HASI for arterial stiffness was significantly less than that of morning PP, suggesting that the recently proposed HASI is a less useful marker for arterial stiffness than is PP in patients with type 2 diabetes. To our knowledge, this is the first report to investigate whether HASI is more strongly associated with PWV and whether it would thus be a more suitable tool than PP for evaluating arterial stiffness in patients with type 2 diabetes.

Schillaci *et al.*[19] suggested that a narrow range of diastolic blood pressure values throughout the 24-h period results in higher AASI values. This is because a narrow range of diastolic blood pressure values flattens the regression line of diastolic on systolic blood pressure. In the same line, for a given range of diastolic blood pressure values, the wider the range of systolic blood pressure values, the flatter the regression line and thereby the higher the AASI value.

PP increases concomitantly with arterial stiffness because the stiffer the aorta is, the faster the reflected pressure wave returns to the heart and superimposes in the forward wave during late systole.[7] The exact pathophysiological meaning of AASI in terms of arterial regulation has not been established. Recently, it was suggested that AASI may be a measure of ventriculo-arterial coupling because it depends on arterial factors and on cardiac factors.[20] Even though many authors consider both PP and AASI as surrogates of arterial stiffness, these parameters may have different physiological meanings from the arterial stiffness, such as PWV. This study indicates that morning PP is a better marker for arterial stiffness than is morning HASI, which has been proposed as a new marker for arterial stiffness.

Qureshi *et al.*[5] have demonstrated that HASI was significantly correlated with aortic PWV and left ventricular mass index. Matsui *et al.*[21] demonstrated that HASI was significantly correlated

Table 1 Clinical characteristics of patients with diabetes

n	332
Gender (male/female)	175/157
Age (years)	65.9 ± 9.7
Duration of diabetes (years)	13.4 ± 9.0
BMI (kg m^{-2})	23.8 ± 3.6
Hemoglobin A1c (%)	7.3 ± 1.1
Total cholesterol (mmol l^{-1})	5.02 ± 0.83
Triglycerides (mmol l^{-1})	1.55 ± 0.97
HDL cholesterol (mmol l^{-1})	1.45 ± 0.41
Smoking (none/past/current)	179/83/70
Alcohol (never/social/everyday)	189/79/64
Retinopathy (NDR/SDR/PDR)	227/67/38
Nephropathy (normo-/micro-/macroalbuminuria)	194/109/29
Neuropathy ($-/+$)	215/117
Cardiovascular disease ($-/+$)	266/66
Current treatment (diet/OHA/insulin)	42/214/76
Antihypertensive medication ($-/+$)	161/171
Pulse wave velocity (cm s^{-1})	1843 ± 347
Clinic systolic blood pressure (mm Hg)	143 ± 20
Clinic diastolic blood pressure (mm Hg)	78 ± 12
Morning systolic blood pressure (mm Hg)	138 ± 18
Morning diastolic blood pressure (mm Hg)	75 ± 10
Morning pulse pressure (mm Hg)	62 ± 14
Morning mean arterial pressure (mm Hg)	96 ± 12
Morning arterial stiffness index	0.67 ± 0.17
Evening systolic blood pressure (mm Hg)	133 ± 17
Evening diastolic blood pressure (mm Hg)	70 ± 10
Evening pulse pressure (mm Hg)	63 ± 14
Evening mean arterial pressure (mm Hg)	91 ± 11
Evening arterial stiffness index	0.61 ± 0.16

Abbreviations: BMI, body mass index; HDL, high-density lipoproteins; NDR, no diabetic retinopathy; OHA, oral hypoglycemic agents; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.
Data are mean ± s.d. or number of subjects.

Table 2 Correlation between home arterial stiffness index or pulse pressure and other variables

	Morning				Evening			
	HASI		PP		HASI		PP	
	r	P	*r*	P	*r*	P	*r*	P
Age	0.135	0.0151	0.374	<0.0001	0.098	0.0794	0.301	<0.0001
Duration of diabetes	−0.010	0.8638	0.187	0.0007	0.117	0.0353	0.232	<0.0001
Body mass index	−0.021	0.7066	−0.056	0.3103	−0.007	0.9004	−0.047	0.3974
Hemoglobin A1c	−0.051	0.3506	0.081	0.1431	−0.010	0.8600	0.096	0.0795
Total cholesterol	−0.026	0.6448	−0.046	0.4160	−0.093	0.0956	−0.024	0.6705
Triglycerides	−0.021	0.7052	−0.056	0.3082	−0.059	0.2875	−0.019	0.7268
HDL cholesterol	0.012	0.8351	0.102	0.0645	−0.069	0.2126	0.071	0.1982
Pulse wave velocity	−0.006	0.9063	0.303	<0.0001	0.184	0.0008	0.354	<0.0001

Abbreviations: HASI, home arterial stiffness index; HDL, high-density lipoprotein; PP, pulse pressure.

Table 3 Multivariate linear regression analysis on pulse wave velocity

| | Morning | | | | Evening | | | |
| | HASI | | PP | | HASI | | PP | |
	β	P	β	P	β	P	β	P
Age	0.216	0.0012	0.154	0.0273	0.219	0.0008	0.178	0.0094
Gender	−0.169	0.0245	−0.143	0.0559	−0.118	0.1083	−0.130	0.0758
Duration of diabetes	0.015	0.8104	−0.014	0.8293	−0.012	0.8517	−0.026	0.6799
Body mass index	−0.110	0.0835	−0.109	0.0833	−0.130	0.0382	−0.119	0.0584
Hemoglobin A1c	0.012	0.8376	0.007	0.9041	0.025	0.6686	0.009	0.8799
Total cholesterol	−0.004	0.9524	0.009	0.8930	0.019	0.7640	0.011	0.8647
Triglycerides	0.015	0.8093	0.023	0.7106	0.016	0.7885	0.014	0.8128
Antihypertensive medication	−0.008	0.8930	−0.032	0.5989	0.008	0.8903	−0.020	0.7469
Smoking	0.016	0.8231	−0.004	0.9543	−0.017	0.8044	−0.031	0.6567
Alcohol	0.102	0.1266	0.118	0.0753	0.160	0.0137	0.152	0.0188
Mean arterial pressure	0.209	0.0012	0.109	0.1456	0.208	0.0007	0.133	0.0618
HASI	−0.040	0.5036	–	–	0.166	0.0058	–	–
PP	–	–	0.179	0.0210	–	–	0.182	0.0144

Abbreviations: HASI, home arterial stiffness index; PP, pulse pressure.
Gender (female = 0, male = 1), presence of antihypertensive medication (no = 0, yes = 1), smoking status (none = 0, past = 1, current = 2) and drinking alcohol (none = 0, social = 1, everyday = 2).
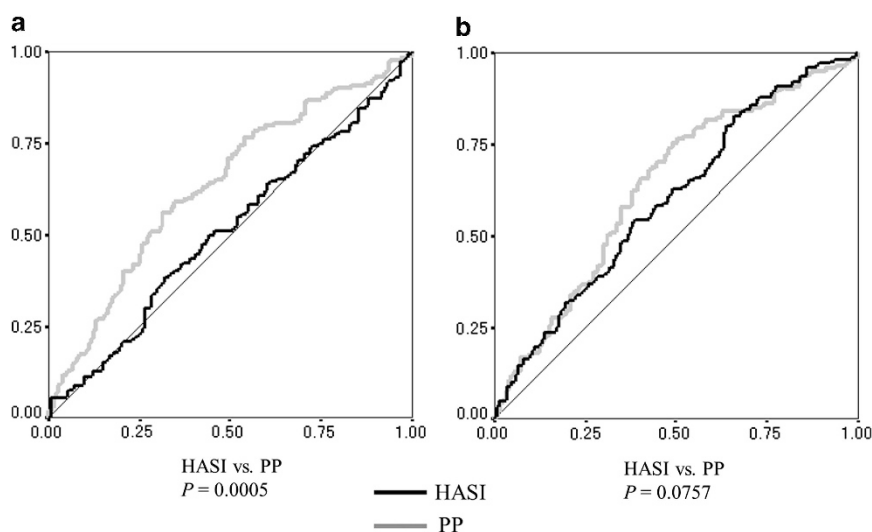

Figure 1 (a) Area under the receiver-operator characteristic curve (AUC) of morning home arterial stiffness index (HASI) and pulse pressure (PP) for arterial stiffness defined as pulse wave velocity $\geqslant 1800\,cm\,s^{-1}$. We compared AUC (95% confidence interval (CI)) between the two groups using the ROCKIT. Value of P was as follows: HASI *vs.* PP, P=0.0005. (b) AUC of evening HASI and PP for arterial stiffness defined as pulse wave velocity $\geqslant 1800\,cm\,s^{-1}$. We compared AUC (95% CI) between the two groups using the ROCKIT. Value of P was as follows: HASI *vs.* PP, P=0.0757.

with carotid atherosclerosis even after adjusting for confounders. On the other hand, Stergiou *et al.*[22] have reported that HASI did not have strength of association to replace AASI for assessing arterial stiffness because HASI was correlated less with age and PP than AASI was. Xu *et al.*[6] reported that the AASI, but not the HASI, is associated with aortic PWV.

HASI is based on blood pressure measurements taken under stabilized conditions. Therefore, this index provides only limited information about the dynamic relationship between systolic blood pressure and diastolic blood pressure. By contrast, AASI is based on measurements taken in ambulatory conditions while patients undertake their usual daily activities. The reason why the AUC of morning HASI for arterial stiffness was significantly less than that of morning

PP while the AUC of evening HASI for arterial stiffness did not differ from that of evening PP has not been clearly determined by this study. The AUC of morning HASI for arterial stiffness was significantly less than that of the AUCs of morning PP, evening HASI and evening PP (data not shown). In addition, the reason why drinking alcohol was independently associated with PWV in multiple regression analysis is not clear. The mean PWV in non-drinkers, social drinkers and everyday drinkers was 1833 ± 330, 1864 ± 374 and 1872 ± 346 cm s^{-1}, respectively (P = 0.6710). In general, light-to-moderate alcohol intake has been reported to be vasculoprotective;[23] however, in a study by Matsumoto *et al.*,[24] light-to-moderate alcohol intake appeared to have a possible vasculoprotective effect in subjects with optimal or normal blood pressure, but the U-shaped relationship was not observed, and

heavy alcohol intake seemed to exert a detrimental effect on the vasculature in subjects with high normal blood pressure or high blood pressure. Most of the patients in the present study had a high normal blood pressure or high blood pressure.

Kikuya et al.[25] reported that HASI predicted cerebral infarction independent of PP and other risk factors in normotensive subjects. Therefore, we evaluated the relationship between HASI and PWV in normotensive patients. Morning HASI was not significantly associated with PWV ($r = 0.083$, $P = 0.5576$), and evening HASI was not also significantly associated with PWV ($r = 0.163$, $P = 0.2442$). Unfortunately, however, the number of normotensive patients was too small ($n = 53$) to adequately evaluate the relationship between HASI and PWV in normotensive patients in this study.

This study has some limitations that require consideration. First, the relatively small number of patients may not be sufficient to conclude that morning HASI is a less suitable tool for evaluating arterial stiffness than is morning PP in patients with type 2 diabetes. Second, it might therefore be argued that HASI, as estimated in this study, provides only limited information about the dynamic relationship of systolic with diastolic blood pressure because HASI is exclusively derived from morning and evening blood pressure measurements, each time measured in triplicate but within a short time interval. Third, for comparing the AUC of HASI or PP for arterial stiffness, we defined arterial stiffness as PWV $\geqslant 1800\,\mathrm{cm\,s^{-1}}$, which is an arbitrary level, because the median value of PWV in this study was $1828\,\mathrm{cm\,s^{-1}}$. If we had defined arterial stiffness as PWV $\geqslant 1600$ or $\geqslant 2000\,\mathrm{cm\,s^{-1}}$, the main findings would have been almost identical (data not shown). Finally, the reproducibility of HASI has not been clarified.

CONCLUSIONS

The AUC of morning HASI for arterial stiffness was significantly less than that of morning PP, suggesting that the recently proposed HASI is a less useful marker for arterial stiffness than is PP in patients with type 2 diabetes. Morning HASI could not be regarded as a reliable substitute for morning PP as a marker for arterial stiffness.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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