Clinical Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2014, Vol. 42(6) 1323–1334

DOI: 10.1177/0300060514548288
imr.sagepub.com
SAGE

Ambulatory arterial stiffness index correlates with ambulatory pulse pressure but not dipping status in patients with grade 1/grade 2 essential hypertension

Tingli Qin[1,*], Hong Jiang[1,*], Yuan Jiao[1], Yuannan Ke[1], Ningling Sun[2], Jiguang Wang[3] and Junren Zhu[4]

Abstract

Objective: To evaluate the relationship between ambulatory arterial stiffness index (AASI) and other parameters derived from ambulatory blood pressure (BP) monitoring, including dipping status, in patients with grade 1/grade 2 hypertension.

Methods: This retrospective analysis included baseline data from Chinese outpatients enrolled into a previous study, who had clinic diastolic BP of 90–109 mmHg and systolic BP <180 mmHg, had undergone 24-h ambulatory BP monitoring and routine blood chemistry investigations, and had estimated glomerular filtration rate (eGFR) data.

Results: Out of 120 patients screened, 87 were included. No significant difference in 24-h AASI was found between dippers and nondippers. The 24-h AASI significantly correlated with age, systolic BP and pulse pressure, and inversely correlated with 24-h diastolic BP variation and eGFR. In dippers and nondippers, AASI correlated with daytime pulse pressure, daytime diastolic BP variation and eGFR; in nondippers, AASI also correlated with 24-h systolic BP and 24-h pulse pressure. The 24-h AASI was significantly associated with 24-h pulse pressure and daytime pulse pressure.

Conclusion: In patients with grade 1/grade 2 essential hypertension, AASI shows a significant correlation with ambulatory pulse pressure.

[1]Department of Cardiology, China-Japan Friendship Hospital, Beijing, China
[2]Department of Cardiology, People's Hospital, Peking University, Beijing, China
[3]Centre for Epidemiological Studies and Clinical Trials, Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[4]Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China
*These authors contributed equally to this work.

Corresponding author:
Yuannan Ke, Department of Cardiology, China-Japan Friendship Hospital, 2 Yinghua Dongjie, Hepingli, Beijing 100029, China.
Email: keyuannan6666@aliyun.com

Keywords
Ambulatory blood pressure monitoring, ambulatory arterial stiffness index, blood pressure variability, morning blood pressure surge, pulse pressure

Date received: 26 December 2013; accepted: 27 July 2014

Introduction

Vascular stiffness is known to be a predictor of adverse cardiovascular outcomes,[1,2] therefore its measurement may be useful in a clinical setting. The 'gold standard' measurement of arterial stiffness, pulse wave velocity,[3] is not commonly used, however, due to the complexity of the equipment required. Thus, there has been substantial research into the development of simpler measures of vascular resistance for more widespread clinical use.

Ambulatory arterial stiffness index (AASI) is a relatively novel estimate of arterial stiffness that is derived from ambulatory blood pressure (BP) monitoring, and is calculated as one minus the regression slope of diastolic BP over systolic BP.[4,5] There is substantial evidence that AASI independently predicts cardiovascular mortality, even in normotensive subjects. For example, AASI has been shown to correlate with target organ damage and glomerular filtration rate (GFR) in patients with essential hypertension,[4,6–9] and with cardiovascular events and mortality,[10,11] including stroke-related mortality.[12] In addition, measurements of AASI have reasonably good reproducibility and repeatability.[13–16]

The biological mechanisms that underlie AASI as a parameter of arterial stiffness, however, remain unclear. From a mathematical standpoint, the possibility exists that assessment of AASI may be confounded by other parameters derived from ambulatory BP monitoring, including BP variation, pulse pressure, nocturnal dipping, and the morning BP surge.[17,18] These measures of variability in BP have been documented by some reports to be prognostic markers of target-organ damage and cardiovascular disease.[19–24]

In addition to AASI, several other factors have been reported to correlate with stiffer vessels in patients with hypertension, including a nondipper pattern, and other markers such as pulse pressure.[25,26] The relationship between these markers and AASI has yet to be clearly defined in patients with essential hypertension. The present authors hypothesized that indicators of arterial stiffness derived from ambulatory BP monitoring might be correlated with each other. The purpose of the present study, therefore, was to evaluate the relationship between measurements of arterial stiffness using AASI, daytime AASI and night-time AASI with other markers of vessel stiffness derived from 24-h ambulatory BP monitoring, including BP variation, pulse pressure, nocturnal dipping, and the morning BP surge, in patients with grade 1/grade 2 essential hypertension.[27]

Patients and methods

Study design and population

The present retrospective study included baseline data obtained from a proportion of the population included in a previously published multicentre, open-label, single-arm, prospective phase IV clinical trial.[28] The original study was conducted between June 2008 and April 2010 in the outpatient clinics of 16 tertiary hospitals in China.[28] Patients from five of these hospitals: China-Japan Friendship Hospital, Beijing; Peking University People's Hospital, Beijing; Ruijin Hospital of Shanghai Jiaotong University School of Medicine, Shanghai; Zhongshan Hospital of Fudan University School of

Medicine, Shanghai; and Guangdong General Hospital, Guangzhou, underwent ambulatory BP monitoring, and were included in the present analyses. The study was approved by the local ethics committees of all five participating hospitals, and written informed consent was provided by all patients. The study followed the Helsinki Declaration and Good Clinical Practice by State Food and Drug Administration.

Inclusion criteria comprised: Chinese outpatients; aged 18–75 years; grade 1/grade 2 essential hypertension with a clinic diastolic BP of 90–109 mmHg and a systolic BP <180 mmHg; no antihypertensive medication taken for at least 1 week prior to the start of the trial. Exclusion criteria included: secondary hypertension; isolated systolic hypertension (systolic BP ≥140 mmHg and diastolic BP <90 mmHg); obesity (body mass index [BMI] ≥30 kg/m^2 or body weight ≥100 kg); use of agents that might influence BP; pregnancy or childbearing potential; impairment of liver function (serum alanine transaminase two times the upper limit of normal); impairment of renal function (serum creatinine ≥1.5 times the upper limit of normal, proteinuria ≥2+ on a dip-stick test); indications for the use of other drugs that may affect BP; hypersensitivity to the study drug;[28] any other conditions that, in the opinion of the investigators, would make enrolment inappropriate.

Eligible patients were consecutively recruited at baseline, at which time all office measurements, routine haematological examinations, routine urinalysis, electrocardiography, and hepatic and renal function tests were performed. Patients who met the exclusion criteria were excluded from the present investigation. Patients then underwent a 2-week placebo run-in period, during which they received placebo medication (Daiichi-Sankyo, Shanghai, China) and no other antihypertensive drugs, to clear the system of any prior medication that may have influenced the results of the original trial.[28]

BP measurements

Heart rate was determined at the baseline visit. Office BP was measured from the right arm, by trained investigators, using a standard mercury sphygmomanometer following European Society of Hypertension (ESH)/European society of Cardiology (ESC) guidlines.[27] Patients were allowed to sit quietly for ≥10 min prior to assessment of BP; three consecutive measurements were made ≥2 min apart, and BP was determined as the mean of the three readings. 24-h ambulatory BP monitoring was performed using a BP monitor (model 90207 and 90217; Spacelabs Healthcare, Snoqualmie, WA, USA) at the end of the 2-week placebo run-in period. The ambulatory BP monitors were set to measure BP every 15 min between 06.01 h and 22.00 h (daytime; patients got up at 06.00 h), and every 30 min between 22.01 h and 06.00 h (night-time; patients went to bed at 22.00 h) using manufacturer-provided software according to ESH/ESC guidelines.[27] Acceptable 24-h ambulatory BP monitoring was defined as continual data collection without interruption, over a monitoring time of ≥22 h, with legible data accounting for ≥80% of the total recordings. Ambulatory BP measurements were used to calculate 24-h AASI, daytime AASI and night-time AASI, defined as one minus the regression slope of diastolic BP over systolic BP.

In addition, patients were divided into two groups for the purpose of analysis according to their dipper profile, as defined by the American Heart Association and following ESH/ESC guidelines:[27] dippers (patients whose nocturnal decrease in systolic BP/diastolic BP was ≥10% of daytime BP) and nondippers (patients whose nocturnal decrease in systolic BP/diastolic BP was <10% of daytime BP).

Laboratory investigations

Venous blood samples (5 ml) were drawn following a ≥8 h fast, for routine blood chemistry investigations: plasma Na^+ and K^+ concentrations, fasting blood glucose, serum creatinine, haemoglobin, and blood urea nitrogen. For plasma samples, blood was collected into vacuum tubes containing 1.5–2.5 mg/ml dipotassium ethylenediaminetetra-acetic acid (2 ml EDTA-K_2 tubes). Samples were then centrifuged at 1 280 g for 10 min at 4°C and the plasma was collected. For serum samples, blood was allowed to stand for 30 min at room temperature to allow clotting. Samples were then centrifuged at 1 280 g for 10 min at 4°C, and the serum collected. Serum and plasma samples were analysed using a regularly calibrated COBAS Mira Plus chemistry analyser (Roche, Basel, Switzerland) according to the manufacturer's instructions. Estimated GFR (eGFR) was calculated using the Modification of Diet in Renal Disease formula:[29]

$$\text{eGFR (ml/min/1.73 m}^2) = 186 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times (-0.74 \text{ if female}).$$

Serum creatinine measured in μmol/l × 0.011312.

Statistical analyses

Data were analysed using SPSS®, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± SD, and qualitative variables as frequency distributions. Categorical variables were analysed using χ^2-test. Differences in continuous variables (such as AASI, age, BMI, systolic BP/diastolic BP, BP variation and blood parameters between dippers and nondippers) were analysed by independent samples *t*-test. Pearson's correlation coefficient was used to estimate the relationship between quantitative variables obtained from ambulatory BP monitoring recordings in all participants. In the dipper and nondipper groups, Partial correlation coefficient was used to estimate the relationship between quantitative variables obtained from ambulatory BP monitoring, including the adjustment variables patient age and BMI. Multiple linear regression analysis was performed using 24-h AASI, daytime AASI and night-time AASI as dependent variables. The enter method was used in a first step to adjust for patient age and BMI, the independent variables (eGFR, office measurements, ambulatory BP, pulse pressure, morning BP surge, variations of 24 h, daytime, and night-time BP) were then included one by one, to avoid colinearity. A P value <0.05 was considered statistically significant. The statistical power, when α was set at 0.05, to identify a significant difference between the dipper and nondipper groups was 0.90 (two-sided), based on the final number of patients included for analyses.

Results

A total of 120 patients, aged 18–75 years, were screened and provided baseline measurements. Of these patients, 24 were withdrawn from the study on the basis of predetermined exclusion criteria, therefore 96 were entered into the 2-week placebo run-in period. A further nine patients were lost due to withdrawal from the study. A total of 87 patients (52 male, 35 female; mean age 51 ± 8 years) completed the study, providing ambulatory BP monitoring readings that were deemed of acceptable quality for analyses (Table 1).

The dipper group comprised 40 patients (46%) and the nondipper group comprised 47 patients (54%) of whom 13 (27.7%) were classed as reverse dippers. There were no significant differences between dipper and nondipper groups in terms of age, sex or BMI. The two groups had similar proportions of grade 1 and grade 2 hypertensive

Table 1. Characteristics of patients with grade 1/grade 2 essential hypertension, assessed at baseline (office and blood measurements) and following a 2-week placebo run-in period (ambulatory measurements).

Variable	All patients $n = 87$	Dipper group $n = 40$	Nondipper group $n = 47$	Statistical significance
Age	51.67 ± 8.72	51.40 ± 7.93	51.89 ± 9.43	NS
Sex, male	52 (59.8)	26 (65.0)	26 (55.3)	NS
Body mass index, kg/m^2	24.41 ± 2.90	25.03 ± 2.81	25.75 ± 2.97	NS
Office systolic BP, mmHg	151.11 ± 10.46	151.76 ± 11.28	150.55 ± 9.80	NS
Office diastolic BP, mmHg	98.80 ± 4.52	98.89 ± 4.31	98.73 ± 4.76	NS
Office heart rate, bpm	74.56 ± 9.64	74.40 ± 10.53	74.70 ± 8.94	NS
24-h systolic BP, mmHg	142.32 ± 12.84	147.20 ± 15.11	138.18 ± 8.74	$P = 0.001$
24-h diastolic BP, mmHg	91.67 ± 7.48	95.18 ± 7.27	88.68 ± 6.32	$P < 0.001$
24-h pulse pressure, mmHg	50.65 ± 10.69	52.02 ± 11.74	49.50 ± 9.68	NS
Daytime systolic BP, mmHg	146.48 ± 13.15	150.22 ± 16.19	143.29 ± 8.86	$P = 0.013$
Daytime diastolic BP, mmHg	94.16 ± 7.77	96.43 ± 7.76	92.22 ± 7.31	$P = 0.011$
Daytime pulse pressure, mmHg	52.32 ± 10.94	53.79 ± 12.36	51.07 ± 9.51	NS
Night-time systolic BP, mmHg	135.45 ± 15.27	142.30 ± 16.49	129.61 ± 11.41	$P < 0.001$
Night-time diastolic BP, mmHg	87.69 ± 9.35	93.26 ± 8.67	82.97 ± 7.08	$P < 0.001$
Night-time pulse pressure, mmHg	47.75 ± 12.17	49.05 ± 13.26	46.64 ± 11.88	NS
24-h systolic BP variation, mmHg	14.15 ± 4.07	13.84 ± 4.17	14.41 ± 4.03	NS
24-h diastolic BP variation, mmHg	11.04 ± 3.89	10.31 ± 3.11	11.66 ± 4.39	NS
Daytime systolic BP variation, mmHg	11.59 ± 4.15	11.59 ± 4.23	11.59 ± 4.13	NS
Daytime diastolic BP variation, mmHg	8.24 ± 2.85	8.16 ± 2.77	8.31 ± 2.94	NS
Night-time systolic BP variation, mmHg	12.58 ± 4.74	12.64 ± 4.27	12.53 ± 5.15	NS
Night-time diastolic BP variation, mmHg	12.03 ± 6.53	11.34 ± 4.97	12.96 ± 7.62	NS
Morning systolic BP surge, mmHg	30.89 ± 16.10	29.55 ± 16.33	32.03 ± 15.99	NS
Morning diastolic BP surge, mmHg	26.99 ± 17.55	26.69 ± 13.53	27.25 ± 20.50	NS
24-h AASI	0.42 ± 0.23	0.46 ± 0.26	0.38 ± 0.20	NS
Daytime AASI	0.46 ± 0.24	0.48 ± 0.22	0.44 ± 0.24	NS
Night-time AASI	0.40 ± 0.36	0.46 ± 0.39	0.34 ± 0.32	NS
Serum creatinine, μmol/l	72.36 ± 16.62	75.51 ± 22.37	74.82 ± 27.53	NS
eGFR, ml/min/1.73 m^2	107.40 ± 25.86	104.54 ± 26.68	106.24 ± 23.48	NS
Blood urea nitrogen, μmol/l	5.11 ± 4.81	4.72 ± 1.59	5.48 ± 6.55	NS
Fasting blood glucose, mmol/l	5.68 ± 1.85	6.05 ± 2.09	5.33 ± 1.54	NS
Plasma K^+, mmol/l	3.99 ± 0.79	4.02 ± 0.81	3.97 ± 0.79	NS
Plasma Na^+, mmol/l	130.41 ± 35.94	131.69 ± 33.19	129.23 ± 38.72	NS
Haemoglobin, mmol/l	135.85 ± 83.69	139.40 ± 36.16	132.49 ± 41.04	NS

Data presented as mean ± SD or *n* (%) patient incidence.

Dipper group, night-time decrease in systolic BP/diastolic BP ≥10% of daytime BP; nondipper group, night-time decrease in systolic BP/diastolic BP <10% of daytime BP.

AASI, ambulatory arterial stiffness index for 24-h, daytime and night-time periods; BP, blood pressure; eGFR, estimated glomerular filtration rate.

NS, no statistically significant differences between dipper versus nondipper groups ($P > 0.05$; Student's *t*-test).

patients: the dipper group comprised 32 with grade 1 and 8 with grade 2 hypertension; the nondipper group comprised 39 with grade 1 and 8 with grade 2 hypertension. The dipper group had significantly higher values for 24-h systolic BP ($P = 0.001$), 24-h diastolic BP ($P < 0.001$), daytime systolic BP ($P = 0.013$), daytime diastolic BP ($P = 0.011$), night-time

systolic BP ($P < 0.001$) and night-time diastolic BP ($P < 0.001$) compared with the nondipper group (Table 1). There were no significant differences, however, between the two groups in terms of mean 24-h AASI, daytime AASI, night-time AASI, or other parameters derived from ambulatory BP monitoring. In addition, there were no significant between-group differences in blood parameters and eGFR (Table 1).

Correlation analyses were undertaken to explore which parameters were associated with 24-h AASI, daytime AASI and night-time AASI (Table 2). The 24-h AASI and daytime AASI were significantly associated with age ($P < 0.05$). The 24-h AASI, daytime AASI and night-time AASI were significantly positively correlated with 24-h systolic BP, 24-h pulse pressure and daytime pulse pressure ($P < 0.05$); 24-h AASI and daytime AASI were significantly associated with night-time systolic BP ($P < 0.05$); 24-h AASI and night-time AASI were significantly correlated with daytime systolic BP ($P < 0.05$); and 24-h AASI was related to night-time pulse pressure ($P < 0.05$). There were no correlations between 24-h AASI, daytime AASI or night-time AASI and 24-h, daytime or night-time diastolic BP; however, all three values negatively correlated with

Table 2. Pearson's correlation coefficient analysis of the associations between ambulatory arterial stiffness index (AASI) and other characteristics, including various parameters obtained from ambulatory blood pressure monitoring in patients with grade 1/grade 2 essential hypertension ($n = 87$).

	AASI values					
	24-h AASI		Daytime AASI		Night-time AASI	
Variable	*r*	Statistical significance	*r*	Statistical significance	*r*	Statistical significance
Age	0.308	$P = 0.004$	0.251	$P = 0.019$	0.109	NS
Body mass index	0.013	NS	0.027	NS	0.105	NS
eGFR	−0.718	$P < 0.001$	−0.567	$P < 0.001$	−0.334	$P < 0.001$
24-h systolic BP	0.313	$P = 0.003$	0.222	$P = 0.039$	0.217	$P = 0.043$
24-h diastolic BP	−0.054	NS	−0.040	NS	−0.025	NS
24-h pulse pressure	0.404	$P < 0.001$	0.278	$P = 0.009$	0.304	$P = 0.004$
Daytime systolic BP	0.311	$P = 0.003$	0.197	NS	0.261	$P = 0.015$
Daytime diastolic BP	−0.161	NS	−0.164	NS	−0.007	NS
Daytime pulse pressure	0.489	$P < 0.001$	0.319	$P = 0.003$	0.353	$P = 0.001$
Night-time systolic BP	0.263	$P = 0.014$	0.229	$P = 0.033$	0.106	NS
Night-time diastolic BP	0.136	NS	0.127	NS	−0.038	NS
Night-time pulse pressure	0.226	$P = 0.035$	0.163	NS	0.189	NS
24-h systolic BP variation	0.014	NS	0.124	NS	0.158	NS
24-h diastolic BP variation	−0.142	NS	−0.236	$P = 0.028$	−0.071	NS
Daytime systolic BP variation	0.021	NS	0.091	NS	−0.071	NS
Daytime diastolic BP variation	−0.230	$P = 0.032$	−0.323	$P = 0.002$	−0.576	$P < 0.001$
Night-time systolic BP variation	−0.036	NS	0.045	NS	0.107	NS
Night-time diastolic BP variation	−0.086	NS	−0.108	NS	0.101	NS
Morning systolic BP surge	−0.132	NS	−0.167	NS	−0.105	NS
Morning diastolic BP surge	0.082	NS	0.051	NS	0.098	NS

BP, blood pressure; eGFR, estimated glomerular filtration rate.
NS, no statistically significant correlation ($P > 0.05$).

daytime diastolic BP variation ($P < 0.05$), and daytime AASI was inversely associated with 24-h diastolic BP variation ($P < 0.05$). In addition, significant negative correlations were found between eGFR and 24-h AASI, daytime AASI and night-time AASI ($P < 0.001$).

Further correlation analyses were undertaken to establish associations between 24-h AASI and various parameters in the dipper and nondipper groups (Table 3). In both the dipper and nondipper groups, 24-h AASI was significantly positively correlated with daytime pulse pressure and daytime diastolic BP variation ($P < 0.05$), and inversely associated with eGFR ($P < 0.05$). In addition, there were significant (but relatively weak) positive associations between 24-h AASI with 24-h systolic BP and 24-h pulse pressure in the nondipper group ($P < 0.05$), but not in the dipper group.

Stepwise linear regression analysis was performed, including AASI as the independent variable, and 24-h pulse pressure, daytime pulse pressure and night-time pulse pressure as the dependent variables. The 24-h AASI was found to significantly correlate with daytime pulse pressure in both the dipper and nondipper groups, and with 24-h pulse pressure in the dipper group.

Table 3. Partial correlation analysis of the associations between 24-h ambulatory arterial stiffness index (AASI) and other characteristics, including various parameters obtained from ambulatory blood pressure monitoring (after adjustment for age and body mass index) in patients with grade 1/grade 2 essential hypertension.

	24-h AASI			
	Dipper group $n = 40$		Nondipper group $n = 47$	
Variable	r	Statistical significance	r	Statistical significance
eGFR	−0.817	$P < 0.001$	−0.637	$P < 0.001$
24-h systolic BP	0.103	NS	0.338	$P = 0.022$
24-h diastolic BP	−0.105	NS	−0.146	NS
24-h pulse pressure	0.216	NS	0.406	$P = 0.005$
Daytime systolic BP	0.132	NS	0.318	$P = 0.031$
Daytime diastolic BP	−0.219	NS	−0.210	NS
Daytime pulse pressure	0.346	$P = 0.031$	0.466	$P = 0.001$
Night-time systolic BP	0.052	NS	0.268	NS
Night-time diastolic BP	0.076	NS	0.023	NS
Night-time pulse pressure	0.012	NS	0.260	NS
24-h systolic BP variation	0.108	NS	0.175	NS
24-h diastolic BP variation	−0.094	NS	−0.118	NS
Daytime systolic BP variation	−0.006	NS	0.203	NS
Daytime diastolic BP variation	−0.332	$P = 0.036$	−0.322	$P = 0.027$
Night-time systolic BP variation	−0.102	NS	0.175	NS
Night-time diastolic BP variation	0.033	NS	−0.191	NS
Morning systolic BP surge	−0.266	NS	0.039	NS
Morning diastolic BP surge	0.201	NS	0.143	NS

BP, blood pressure; eGFR, estimated glomerular filtration rate.
NS, no statistically significant correlation ($P > 0.05$).

Table 4. Stepwise linear regression analysis of the correlation between ambulatory arterial stiffness index (AASI) and pulse pressure profiles in patients with grade 1/grade 2 essential hypertension ($n = 87$).

	24-h AASI		Daytime AASI		Night-time AASI	
Variable	ß	Statistical significance	ß	Statistical significance	ß	Statistical significance
All						
24-h pulse pressure	−0.016	$P = 0.019$	0.007	$P = 0.003$	–	–
Daytime pulse pressure	0.026	$P < 0.001$	–	–	–	–
Night-time pulse pressure	–	–	–	–	0.012	$P = 0.001$
Dipper						
24-h pulse pressure	−0.045	$P < 0.001$	–	–	–	–
Daytime pulse pressure	0.052	$P < 0.001$	0.007	$P = 0.047$	0.091	$P = 0.003$
Night-time pulse pressure	–	–	–	–	−0.088	$P < 0.001$
Nondipper						
24-h pulse pressure	–	–	–	–	–	–
Daytime pulse pressure	0.008	$P = 0.006$	–	–	–	–
Night-time pulse pressure	–	–	0.007	$P = 0.029$	0.009	$P = 0.021$

The daytime AASI was found to significantly correlate with daytime pulse pressure in the dipper group, and with night-time pulse pressure in nondipper group. The night-time AASI was found to significantly correlate with daytime pulse pressure in the dipper group, and with night-time pulse pressure in both the dipper and nondipper groups (Table 4).

Discussion

The main findings of the present study were that AASI did not differ between patients in the dipper and nondipper groups, and that pulse pressure showed a clear association with AASI.

Despite substantial evidence that AASI may be a useful indicator of arterial stiffness,[30] its use as an independent measure of vascular stiffness, and the extent to which it is influenced by other parameters not directly related to arterial compliance, remain under debate. The basis of AASI is that an increase in systolic BP in a stiff artery will be accompanied by a smaller increase (or even decrease) in diastolic BP.[15] Mathematical considerations indicate, however, that AASI may be influenced by other factors, including variations in 24-h diastolic BP. The present study revealed that AASI was associated with several parameters derived from ambulatory BP monitoring, including 24-h, daytime and night-time systolic BP, and 24-h, daytime and night-time pulse pressure. In agreement with the present data, AASI has previously been observed to positively correlate with 24-h systolic BP, daytime systolic BP, night-time systolic BP, 24-h pulse pressure, daytime pulse pressure and night-time pulse pressure,[31] while a meta-analysis of cross-sectional and longitudinal studies found that AASI was independently associated with systolic BP and 24-h pulse pressure.[15] Other studies have reported associations between AASI and pulse pressure.[5,17,32] Additional data supporting AASI as a reliable assessment of vascular stiffness include the findings of its association with other measures of vascular compliance, such as carotid intima-media thickness, pulse wave velocity and augmentation index.[5,13,15,32–34] The observations that AASI predicts

cardiovascular and stroke mortality over and beyond pulse pressure,[12] and that renal disease increases AASI (but not pulse pressure) in patients with hypertension,[35] indicate that AASI is not merely reflecting alterations in pulse pressure.

Some authors have argued, however, that AASI is dependent on the degree of nocturnal BP fall, and is only weakly associated with pulse wave velocity.[18,36] In untreated patients with hypertension, one study found that AASI was higher in dippers (0.44 ± 0.20) than in nondippers (0.29 ± 0.15), and was inversely correlated with nocturnal falls in systolic BP and diastolic BP; in contrast, there was no association between pulse wave velocity and nocturnal BP fall.[18] Various other studies have identified inverse associations between AASI and nocturnal decline in BP.[17,31] Additional correlations have been found between AASI and indices of BP variability. For example, in one study, pulse pressure variability, systolic BP variability, diastolic BP variability and nondipper status were determined to be independent predictors of AASI, suggesting that AASI is a parameter that reflects BP variability as well as arterial stiffness.[17] Furthermore, systolic BP variation and diastolic BP variation have been shown to correlate with intima-media thickness, pulse wave velocity and AASI, with 24-h diastolic BP variation having a significant association with AASI in a multiple regression analysis.[37] Similarly, AASI has been found to negatively correlate with the morning surge in diastolic BP, daytime diastolic BP, 24-h mean arterial pressure variability, and nocturnal dips in systolic BP, diastolic BP and mean arterial pressure.[31] These data are broadly consistent with the observations in the present study. Interestingly, however, the values of AASI measured in the present study were not significantly different between the dipper and nondipper groups, perhaps suggesting that although BP variability is related to AASI, dipping status is not a major determinant in patients with grade 1/grade 2 hypertension.

The present study found that despite having similar grades of hypertension, patients in the dipper group had significantly higher values for 24-h, daytime and night-time systolic BP, and 24-h, daytime and night-time diastolic BP, than those in the nondipper group. In addition to positive and negative associations with age and eGFR, respectively, 24-h AASI showed positive correlations with 24-h and daytime systolic BP, and 24-h, daytime and night-time pulse pressure. No significant associations were evident between 24-h AASI and measures of BP variation, except for a weak inverse correlation with daytime diastolic BP variation. In subgroup analysis, 24-h AASI was correlated with eGFR, daytime pulse pressure and daytime diastolic BP variation in both dipper and nondipper groups, while additional associations with 24-h systolic BP and 24-h pulse pressure were observed for the nondipper group. Overall, AASI was most strongly correlated with measures of pulse pressure, and was not associated with most measures of BP variation, except for daytime diastolic BP variation. These data shed further light on the associations between AASI and other parameters derived from ambulatory BP monitoring, in patients with grade 1/grade 2 hypertension.

In the present study, the mean value of AASI was 0.42 ± 0.23. AASI has been reported to be higher in patients with hypertension (0.49 ± 0.17) than in normotensive patients (0.36 ± 0.14).[38] In addition, AASI appears be higher in patients with hypertension and chronic renal disease than in those without renal chronic disease,[35] and is also increased in patients with diabetes,[32] acromegaly[38] and high haemoglobin levels.[39] The finding in the present study that AASI correlated with age was in keeping with numerous investigations that observed the same phenomenon in patients with hypertension.[5,15,17,18,32–35]

The association between a higher AASI and impaired renal function, determined by eGFR, was an additional relevant finding of the present study. There is some disagreement in the literature concerning the correlation between AASI and eGFR. For example, some investigators have observed no correlation between these parameters,[13,35] some a weak correlation,[40] and others a clear negative association.[6,11] It is perhaps of interest to note that nondipping status and 24-h systolic BP variation have also been reported to correlate with lower eGFR.[41,42] In patients with hypertension, age was an independent predictor of low eGFR.[42]

The present results are limited by the fact that this was a retrospective analysis of a subset of patients taken from a different study, in which patients with isolated systolic hypertension (systolic BP $\geq$140 mmHg and diastolic BP <90 mmHg) were required to be excluded.[28] Isolated systolic hypertension may be indicative of arterial stiffness, and in elderly patients, arterial stiffness has been directly implicated in isolated systolic hypertension, therefore, the exclusion of such patients may have biased the results.

In conclusion, the present study found that in a cohort of patients with grade 1/grade 2 essential hypertension, AASI did not differ significantly between patients with a dipper and nondipper status. Significant correlations were observed, however, between AASI and certain parameters reflecting pulse pressure, systolic BP, and variability in diastolic BP. The clear positive correlation between AASI and ambulatory pulse pressure indicates a clinical potential for AASI as an index of arterial stiffness in the monitoring the adverse cardiovascular outcomes, in patients with grade 1/grade 2 essential hypertension.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Hansen TW, Staessen JA, Torp-Pedersen C, et al. Ambulatory arterial stiffness index predicts stroke in a general population. *J Hypertens* 2006; 24: 2247–2253.
2. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236–1241.
3. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27: 2588–2605.
4. Dolan E, Thijs L, Li Y, et al. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. *Hypertension* 2006; 47: 365–370.
5. Li Y, Wang JG, Dolan E, et al. Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. *Hypertension* 2006; 47: 359–364.
6. García-García A, Gómez-Marcos MA, Recio-Rodriguez JI, et al. Relationship between ambulatory arterial stiffness index and subclinical target organ damage in hypertensive patients. *Hypertens Res* 2011; 34: 180–186.
7. Leoncini G, Ratto E, Viazzi F, et al. Increased ambulatory arterial stiffness index is associated with target organ damage in primary hypertension. *Hypertension* 2006; 48: 397–403.
8. Mulè G, Cottone S, Cusimano P, et al. Inverse relationship between ambulatory arterial stiffness index and glomerular filtration rate in arterial hypertension. *Am J Hypertens* 2008; 21: 35–40.
9. Triantafyllidi H, Tzortzis S, Lekakis J, et al. Association of target organ damage with three arterial stiffness indexes according to blood pressure dipping status in untreated hypertensive patients. *Am J Hypertens* 2010; 23: 1265–1272.

10. Kikuya M, Ohkubo T, Satoh M, et al. Prognostic significance of home arterial stiffness index derived from self-measurement of blood pressure: the Ohasama Study. *Am J Hypertens* 2012; 25: 67–73.
11. Muxfeldt ES, Cardoso CR, Dias VB, et al. Prognostic impact of the ambulatory arterial stiffness index in resistant hypertension. *J Hypertens* 2010; 28: 1547–1553.
12. Kikuya M, Staessen JA, Ohkubo T, et al. Ambulatory arterial stiffness index and 24-hour ambulatory pulse pressure as predictors of mortality in Ohasama, Japan. *Stroke* 2007; 38: 1161–1166.
13. Boesby L, Thijs L, Elung-Jensen T, et al. Ambulatory arterial stiffness index in chronic kidney disease stage 2-5. Reproducibility and relationship with pulse wave parameters and kidney function. *Scand J Clin Lab Invest* 2012; 72: 304–312.
14. Dechering DG, van der Steen MS, Adiyaman A, et al. Reproducibility of the ambulatory arterial stiffness index in hypertensive patients. *J Hypertens* 2008; 26: 1993–2000.
15. Kollias A, Stergiou GS, Dolan E, et al. Ambulatory arterial stiffness index: a systematic review and meta-analysis. *Atherosclerosis* 2012; 224: 291–301.
16. Stergiou GS, Kollias A, Rarra VC, et al. Ambulatory arterial stiffness index: reproducibility of different definitions. *Am J Hypertens* 2010; 23: 129–134.
17. Lee HT, Lim YH, Kim BK, et al. The relationship between ambulatory arterial stiffness index and blood pressure variability in hypertensive patients. *Korean Circ J* 2011; 41: 235–240.
18. Schillaci G, Parati G, Pirro M, et al. Ambulatory arterial stiffness index is not a specific marker of reduced arterial compliance. *Hypertension* 2007; 49: 986–991.
19. Birkenhäger AM and van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. *Neth J Med* 2007; 65: 127–131.
20. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005; 46: 156–161.
21. Kario K, Ishikawa J, Eguchi K, et al. Sleep pulse pressure and awake mean pressure as independent predictors for stroke in older hypertensive patients. *Am J Hypertens* 2004; 17: 439–445.
22. Kikuya M, Ohkubo T, Metoki H, et al. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension* 2008; 52: 1045–1050.
23. Mancia G and Parati G. Ambulatory blood pressure monitoring and organ damage. *Hypertension* 2000; 36: 894–900.
24. Parati G and Valentini M. Prognostic relevance of blood pressure variability. *Hypertension* 2006; 47: 137–138.
25. Jerrard-Dunne P, Mahmud A and Feely J. Ambulatory arterial stiffness index, pulse wave velocity and augmentation index—interchangeable or mutually exclusive measures? *J Hypertens* 2008; 26: 529–534.
26. Lekakis JP, Zakopoulos NA, Protogerou AD, et al. Arterial stiffness assessed by pulse wave analysis in essential hypertension: relation to 24-h blood pressure profile. *Int J Cardiol* 2005; 102: 391–395.
27. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 2013; 31: 1925–1938.
28. Wang JG, Sun NL, Ke YN, et al. Long-term efficacy of olmesartan medoxomil in Chinese hypertensive patients as assessed by clinic, ambulatory and home blood pressure measurements. *Clin Drug Investig* 2012; 32: 729–734.
29. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.
30. Xu TY, Li Y, Fan WX, et al. Ambulatory (AASI), but not home (HASI), arterial stiffness index is associated with aortic pulse wave velocity. *Hypertens Res* 2011; 34: 402–403.

31. Liu Z, Hesse C, Curry TB, et al. Ambulatory arterial stiffness index is not correlated with the pressor response to laboratory stressors in normotensive humans. *J Hypertens* 2009; 27: 763–768.
32. Gómez-Marcos MA, Recio-Rodríguez JI, Patino-Alonso MC, et al. Relationship between intima-media thickness of the common carotid artery and arterial stiffness in subjects with and without type 2 diabetes: a case-series report. *Cardiovasc Diabetol* 2011; 10: 3.
33. Bastos JM, Bertoquini S and Polónia J. Prognostic significance of ambulatory arterial stiffness index in hypertensives followed for 8.2 years: its relation with new events and cardiovascular risk estimation. *Rev Port Cardiol* 2010; 29: 1287–1303.
34. Gómez-Marcos MA, Recio-Rodríguez JI, Patino-Alonso MC, et al. Ambulatory arterial stiffness indices and target organ damage in hypertension. *BMC Cardiovasc Disord* 2012; 12: 1.
35. Gismondi RA, Neves MF, Oigman W, et al. Ambulatory arterial stiffness index is higher in hypertensive patients with chronic kidney disease. *Int J Hypertens* 2012; 2012: 178078.
36. Baumann M, Dan L, Nürnberger J, et al. Association of ambulatory arterial stiffness index and brachial pulse pressure is restricted to dippers. *J Hypertens* 2008; 26: 210–214.
37. García-García Á, García-Ortiz L, Recio-Rodríguez JI, et al. Relationship of 24-h blood pressure variability with vascular structure and function in hypertensive patients. *Blood Press Monit* 2013; 18: 101–106.
38. Dassie F, Grillo A, Carretta R, et al. Ambulatory arterial stiffness indexes in acromegaly. *Eur J Endocrinol* 2012; 166: 199–205.
39. Chen H, Hua Q and Hou H. Association of hemoglobin with ambulatory arterial stiffness index in untreated essential hypertensive patients without anemia. *Intern Med* 2011; 50: 2759–2765.
40. Wang Y, Hu Y, Li Y, et al. Association of renal function with the ambulatory arterial stiffness index and pulse pressure in hypertensive patients. *Hypertens Res* 2012; 35: 201–206.
41. Kastarinen H, Vasunta RL, Ukkola O, et al. Glomerular filtration rate is related to dipping pattern in ambulatory blood pressure monitoring—a cross-sectional population-based study. *J Hum Hypertens* 2010; 24: 247–253.
42. Manios E, Tsagalis G, Tsivgoulis G, et al. Time rate of blood pressure variation is associated with impaired renal function in hypertensive patients. *J Hypertens* 2009; 27: 2244–2248.