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# Ambulatory Arterial Stiffness Index Derived From 24-Hour Ambulatory Blood Pressure Monitoring

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**Abstract**—We hypothesized that 1 minus the slope of diastolic on systolic pressure during 24-hour ambulatory monitoring (ambulatory arterial stiffness index [AASI]) might reflect arterial stiffness. We compared AASI with established measures of arterial stiffness and studied its distribution in Chinese and European populations. We used 90207 SpaceLabs monitors and the SphygmoCor device to measure AASI, central and peripheral pulse pressures, the central (CAIx) and peripheral (PAIx) systolic augmentation indexes, and aortic pulse wave velocity. In 166 volunteers, the correlation coefficient between AASI and pulse wave velocity was 0.51 ( $P < 0.0001$ ). In 348 randomly recruited Chinese subjects, AASI correlated ( $P < 0.0001$ ) with CAIx ( $r = 0.48$ ), PAIx ( $r = 0.50$ ), and central pulse pressure ( $r = 0.50$ ). AASI increased with age and mean arterial pressure but decreased with body height. Both before and after adjustment for arterial wave reflections by considering height and heart rate as covariates, AASI correlated more ( $P < 0.0001$ ) closely with CAIx and PAIx than 24-hour pulse pressure. Among normotensive subjects, the 95th percentile of AASI was 0.55 in Chinese and 0.57 in 1617 Europeans enrolled in the International Database on Ambulatory Blood Pressure Monitoring. The upper boundary of the 95% prediction interval of AASI in relation to age ranged from 0.53 at 20 years to 0.72 at 80 years. In conclusion, AASI is a new index of arterial stiffness that can be easily measured under ambulatory conditions. Pending additional validation in outcome studies, normal values of AASI are probably  $< 0.50$  and  $0.70$  in young and older subjects, respectively. (*Hypertension*. 2006;47:359-364.)

**Key Words:** blood pressure monitoring, ambulatory ■ arteries ■ blood pressure ■ epidemiology ■ population

Stiffening of large arteries predicts adverse cardiovascular outcomes.<sup>1-3</sup> Until now, measurements of arterial stiffness require the use of complex ultrasound equipment or applanation tonometry at the level of the peripheral arteries with the subjects in the supine or sitting position.<sup>4</sup> The QKD approach was the first attempt to estimate arterial compliance under ambulatory conditions by measuring the time interval between the Q-wave on the ECG and the disappearance of the Korotkoff sounds at the brachial artery during cuff deflation.<sup>5</sup>

In 1914, MacWilliam and Melvin<sup>6</sup> wrote that loss of elasticity in the arterial system influences the height of the diastolic pressure and its relation to systolic pressure. Along these lines, we hypothesized that the slope of diastolic on systolic pressure during ambulatory monitoring might be a measure of arterial stiffness. We tested this hypothesis in untreated volunteers and in a Chinese population sample. In addition, we compared our findings in Chinese with those in the Belgian and Irish subjects enrolled in the International Database of Ambulatory Blood Pressure Monitoring.<sup>7</sup> In a

companion article,<sup>8</sup> we demonstrate that ambulatory arterial stiffness index (AASI) predicts cardiovascular mortality in hypertensive patients and provides prognostic information complementary to pulse pressure, independent of mean arterial pressure.

## Methods

### Pilot Study in Volunteers

Via Ruijin Hospital in Shanghai, we recruited 166 volunteers, not treated for hypertension, with a minimum age of 20 years. We programmed oscillometric SpaceLabs 90207 monitors (SpaceLabs Inc)<sup>9</sup> to obtain blood pressure readings at intervals of 20 minutes from 8:00 AM until 10:00 PM and 45 minutes from 10:00 PM to 8:00 AM. From individual 24-hour recordings, we computed the regression slope of diastolic pressure on systolic blood pressure. We defined the AASI as 1 minus the regression slope. We did not force the slope through the origin. We measured carotid-femoral pulse wave velocity using a high-fidelity SPC-301 micromanometer (Millar Instruments, Inc) interfaced with a laptop computer running the SphygmoCor software, version 6.31 (AtCor Medical Pty Ltd).<sup>10</sup> The

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From the Centre for Epidemiological Studies and Clinical Trials (Y.L., J.G.W., P.J.G., H.F.G., D.L.Z.), Ruijin Hospital, Shanghai Institute of Hypertension, Shanghai Second Medical University, Shanghai, China; Study Coordinating Centre (T.N., J.A.S.), Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Disease, University of Leuven, Belgium; ADAPT Centre and Blood Pressure Unit, Beaumont Hospital, and the Department of Clinical Pharmacology (E.D., A.S., E.O.B.), Royal College of Surgeons in Ireland, Dublin, Ireland.

Correspondence to Jan A. Staessen, Study Coordinating Centre, Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, Campus Gasthuisberg, University of Leuven, Herestraat 49, B-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be  
Reprint requests to Ding-Liang Zhu, Ruijin Hospital, Shanghai Institute of Hypertension, Ruijin Second Road 197, 20025 Shanghai, China. E-mail zhudingliang@sibs.ac.cn

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Ethics Committee of Shanghai Second Medical University approved the study. All of the participants gave informed written consent.

### Chinese Population Study

We randomly selected 6 villages from the JingNing County, a rural area  $\approx$ 300 miles south of Shanghai. The minimum age for participation was 12 years. At a home visit, trained observers administered a standardized questionnaire. After the subjects had rested for 5 minutes in the sitting position, the observers obtained 5 consecutive auscultatory blood pressure readings, which were averaged for analysis. Mean arterial pressure was diastolic pressure plus one third of pulse pressure. Hypertension was defined as a conventional blood pressure averaging  $\geq$ 140 mm Hg systolic or 90 mm Hg diastolic or as the use of antihypertensive drugs.<sup>11</sup>

Of 509 participants (response rate 61.7%), 348 had their ambulatory blood pressure and vascular properties measured on the same day. We determined AASI as in the volunteers. Immediately before the ambulatory blood pressure recordings, the subjects rested for 15 minutes in the supine position. A single observer recorded the radial arterial waveform at the dominant arm with the SphygmoCor device. During the 8-second recordings, systolic and diastolic variability had to be  $<$ 5% with a pulse wave signal  $>$ 80 mV. From the radial signal, the SphygmoCor software calculates the aortic pulse wave by means of a transfer function.<sup>12</sup> The radial and aortic augmentation indexes were the ratios of the second to the first shoulder of the systolic upstroke.

### Comparison With an International Database

To test the external validity of our findings in Chinese subjects and to determine a clinical reference frame for AASI, we investigated the Belgian and Irish subjects enrolled in the International Database of Ambulatory Blood Pressure Monitoring.<sup>7</sup> The conventional blood pressure was the average of 3 auscultatory readings obtained at the subjects' homes<sup>13</sup> or in the office.<sup>14</sup> We recorded the 24-hour ambulatory blood pressure using oscillometric 90202 or 90207 SpaceLabs devices<sup>9,15</sup> and computed AASI as before.

### Statistical Methods

For database management and statistical analyses, we used SAS software, version 8.2 (SAS Institute Inc). Departure from normality was evaluated by Shapiro-Wilk's statistic<sup>16</sup> and skewness by the computation of the coefficient of skewness, that is the third moment about the mean divided by the cube of the SD.<sup>17</sup> Our statistical methods also included the Student *t* test, the  $\chi^2$  statistic, and single and multiple linear regression. We performed multivariate analysis of variance to test the null hypothesis of no differences between the parameters of regression equations.<sup>18</sup>

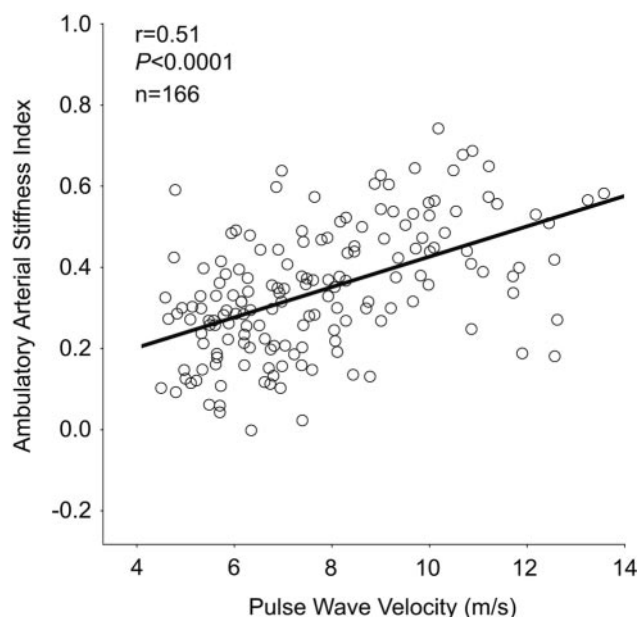
## Results

### Pilot Study in Volunteers

The mean ( $\pm$ SD) age of the 69 men and 97 women volunteers was  $48.2 \pm 19.3$  years (range, 22.3 to 83.2). Their 24-hour blood pressure was  $119.7 \pm 13.8$  mm Hg systolic and  $75.0 \pm 8.6$  mm Hg diastolic. Pulse wave velocity averaged  $7.8 \pm 2.1$  m/s. We found a close relation between AASI and pulse wave velocity (Figure 1), which was consistent in women ( $r=0.58$ ;  $P<0.0001$ ) and men ( $r=0.38$ ;  $P=0.002$ ) and in young ( $<$ 40 years,  $n=73$ ,  $r=0.26$ ;  $P=0.02$ ) and older adults ( $\geq$ 40 years,  $n=93$ ,  $r=0.25$ ;  $P=0.02$ ).

### Chinese Population Study

Among 189 women and 159 men, mean age ( $46.1 \pm 15.5$  years), systolic and diastolic blood pressure measured at home ( $128.9 \pm 24.0/79.8 \pm 12.0$  mm Hg), the prevalence of hypertension (32.8%), the proportion of subjects on antihypertensive medications (14.1%), and the concentration of



**Figure 1.** Relation between the AASI and carotid-femoral pulse wave velocity in 166 volunteers.

serum cholesterol ( $4.91 \pm 1.06$  mmol/L) were similar. Of the 49 subjects who took antihypertensive medications, 32 (9.2%) were on diuretics, 14 (4.0%) on calcium channel blockers, 9 (2.6%) on angiotensin-converting enzyme inhibitors, 2 (0.6%) on  $\beta$ -blockers, and 18 (5.2%) on other antihypertensive drugs. Alcohol intake (74.2% versus 22.8%) and smoking (58.5% versus 0%) were more frequent among men than women. Only 1 patient was in atrial fibrillation and had an average 24-hour heart rate of 74 bpm. Table 1 provides additional information by gender on the anthropometric characteristics, the 24-hour ambulatory recordings, and the SphygmoCor measurements.

Both AASI and the within-subject slope of diastolic on systolic blood pressure ( $\beta$ ) were normally distributed. Table 2

**TABLE 1. Characteristics of the Study Population**

Characteristic	Women (n=189)	Men (n=159)
Age, y	45.6 $\pm$ 14.6	46.7 $\pm$ 16.5
Anthropometric measurements		
Body height, cm	151.4 $\pm$ 5.8*	160.9 $\pm$ 6.3
Body weight, kg	53.1 $\pm$ 8.8*	57.3 $\pm$ 10.1
Body mass index, kg/m <sup>2</sup>	23.1 $\pm$ 3.1*	22.0 $\pm$ 3.0
24-hour ambulatory recordings		
Systolic pressure, mm Hg	119.8 $\pm$ 16.8	121.8 $\pm$ 13.3
Diastolic pressure, mm Hg	76.3 $\pm$ 10.0	77.9 $\pm$ 9.3
Pulse pressure, mm Hg	43.5 $\pm$ 10.0	43.9 $\pm$ 7.3
AASI	0.38 $\pm$ 0.18*	0.33 $\pm$ 0.15
Pulse rate, bpm	72.6 $\pm$ 7.6	71.9 $\pm$ 9.6
SphygmoCor measurements		
Central augmentation index	1.42 $\pm$ 0.24*	1.29 $\pm$ 0.27
Peripheral augmentation index	0.83 $\pm$ 0.19*	0.73 $\pm$ 0.23
Central pulse pressure, mm Hg	39.2 $\pm$ 17.8	37.3 $\pm$ 15.4

Plus-minus values are mean $\pm$ SD.

\*Indicates significant sex difference ( $P<0.01$ ).

**TABLE 2. Distributions of the AASI, Slope of Diastolic on Systolic Pressure, and the Ratio of Pulse Pressure to Systolic Pressure in 348 Chinese Subjects**

Statistic	AASI	Slope of Diastolic on Systolic Pressure	Ratio of Pulse Pressure to Systolic Pressure
Mean	0.3566	0.6435	0.3605
SD	0.1681	0.1681	0.0425
Minimum	-0.1023	0.1757	0.2604
Maximum	0.8243	1.1023	0.5577
Skewness	0.0607	-0.0607	0.6486
Kurtosis	-0.2079	-0.2079	1.4239
Test statistics			
Shapiro-Wilk's W	0.9964 ( $P=0.62$ )	0.9964 ( $P=0.62$ )	0.9771 ( $P<0.001$ )
Coefficient of skewness	0.46 ( $P=0.32$ )	-0.46 ( $P=0.68$ )	4.90 ( $P<0.001$ )

illustrates the reciprocity of their distributions, which is inherent to the definition of AASI. Across subjects, as  $\beta$  increased, the intercept of the regression line used in the derivation of AASI became smaller with a correlation coefficient between intercept and slope close to unity. The formula for AASI can be rewritten as (pulse pressure + intercept) divided by systolic pressure. We, therefore, also studied the ratio of pulse pressure to systolic pressure. As exemplified by Shapiro-Wilk's statistic and the coefficient of skewness, the distribution of this ratio, which does not account for the individual variation in the intercept (or  $\beta$ ), was skewed with a long upper tail and significantly deviated from normality.

AASI increased with age and mean arterial pressure but decreased with body height (Figure 2). In stepwise regression (Table 3), sex, age, mean arterial pressure, and body height were consistent and independent determinants of AASI, as well as the central and peripheral systolic augmentation indexes. The 24-hour heart rate was inversely and independently correlated with systolic augmentation but not with AASI (Table 3). With these 5 covariates in the models, serum cholesterol, smoking, and alcohol intake did not contribute to the variability in the 3 vascular measurements. After adjustment for covariates (Table 3), AASI remained significantly higher in women than men (0.37 versus 0.34;  $P=0.05$ ) and in hypertensive patients compared with normotensive subjects (0.45 versus 0.31;  $P<0.0001$ ).

In all of the subjects, AASI closely correlated with the central and peripheral systolic augmentation indexes and central pulse pressure both before (Figure 3 and Table 4) and after (Table 4) adjustment for body height and the 24-hour heart rate. With and without adjustment, AASI correlated more closely with central and peripheral systolic augmentation than the 24-hour pulse pressure. In subjects <40 years of age, there was no relation of these vascular measurements with the 24-hour pulse pressure, whereas the correlations with AASI remained significant (Table 4). After removing the 49 subjects on antihypertensive medication from the analysis, these results remained consistent.

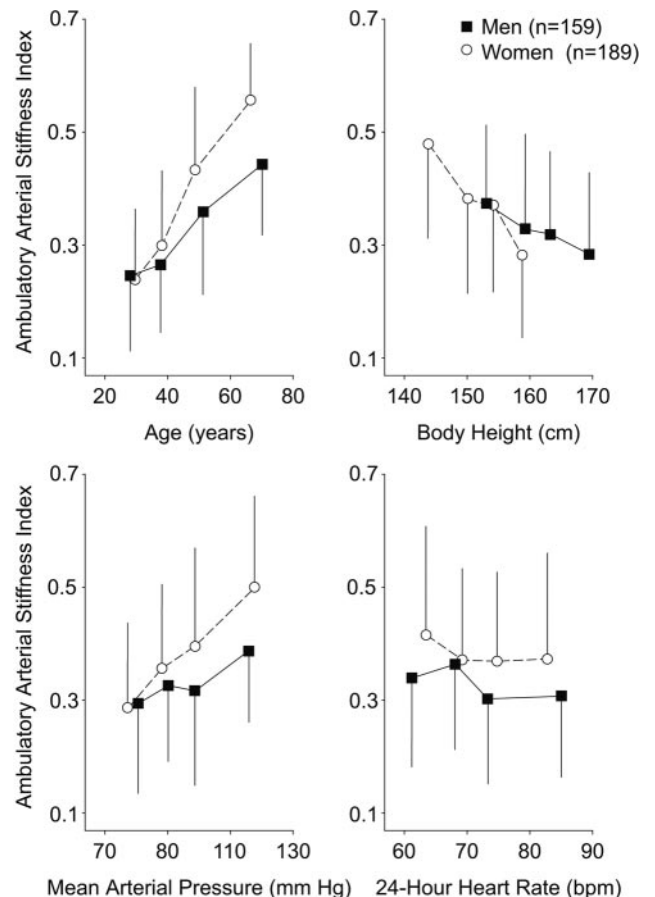
**Analysis of the International Database**

Consistent with our findings in Chinese subjects, AASI increased with hypertension in Belgian and Irish subjects (Figure 4A and 4B). In normotensive Chinese and Europeans,

the 95th percentiles of AASI were 0.55 and 0.57, respectively. In the 3 populations combined (Figure 4C), AASI increased with age. The upper boundary of the 95% confidence band for individual prediction was 0.53 at 20 years and 0.72 at 80 years.

**Discussion**

An article published in 1914 already highlighted the physiological meaning of the relation between diastolic and systolic



**Figure 2.** The AASI in women (○) and men (●). Plotted values are means (vertical lines denote SD) in sex-specific quartiles of age, mean arterial pressure, body height, and 24-hour ambulatory heart rate.

TABLE 3. Correlates of the Arterial Stiffness Indexes

Covariates	Central Augmentation Index		Peripheral Augmentation Index		AASI	
	$\beta \pm SE$	<i>P</i>	$\beta \pm SE$	<i>P</i>	$\beta \pm SE$	<i>P</i>
Age (+10 y)	0.079 $\pm$ 0.008	<0.001	0.068 $\pm$ 0.006	<0.001	0.055 $\pm$ 0.005	<0.001
Mean arterial pressure (+10 mm Hg)	0.026 $\pm$ 0.007	<0.001	0.024 $\pm$ 0.006	<0.001	0.015 $\pm$ 0.005	0.004
Body height (+10 cm)	-0.046 $\pm$ 0.018	0.01	-0.035 $\pm$ 0.015	0.02	-0.026 $\pm$ 0.013	0.04
24-hour pulse rate (+10 bpm)	-0.073 $\pm$ 0.012	<0.001	-0.052 $\pm$ 0.009	<0.001	-0.010 $\pm$ 0.008	0.24
Sex (1, men; 2, women)	0.099 $\pm$ 0.026	<0.001	0.089 $\pm$ 0.021	<0.001	0.037 $\pm$ 0.019	0.05

$\beta$  ( $\pm SE$ ) is the partial regression coefficient.

blood pressure.<sup>6</sup> The authors stated that the left ventricle ejecting blood into a normally elastic arterial system produces lower diastolic and systolic pressures than what would be present in stiffened vessels. Moreover, they also recognized that stiffening of the large arteries would decrease diastolic blood pressure relative to systolic pressure.<sup>6</sup> Building on these hemodynamic principles and making use of the large diurnal variability in blood pressure,<sup>19,20</sup> we conceived AASI as a novel index of vascular stiffness by computing the slope of diastolic on systolic pressure ( $\beta$ ) from 24-hour ambulatory recordings. We did not force the regression line through the origin (intercept=0), because during diastole when flow drops to zero, this does not occur for blood pressure.<sup>21</sup> Next, we subtracted  $\beta$ , which is dimensionless (mm Hg/mm Hg), from unity. By doing so, we ensured that the correlations with known determinants of arterial function had the same sign for AASI and the other measures of arterial stiffness considered in this article.<sup>22-24</sup> According to the basic assumptions underlying regression analysis, the parameters of linear regression models are normally distributed. In line with this concept, the distributions of  $\beta$  and AASI were Gaussian. In contrast, the ratio of pulse pressure to systolic blood pressure, which does not account for the intraindividual variation in  $\beta$  (or intercept), was significantly skewed to the left. AASI and the ratio of pulse pressure to systolic blood pressure are, therefore, not equivalent. This observation and established physiological principles<sup>6,21</sup> support our current hypothesis that AASI is an integrated measure, which is characteristic for an individual and which reflects the combined effects of left ventricular

ejection, active and passive components of arterial stiffness, and the reflection of the arterial pulse wave.<sup>6,21</sup>

We found that AASI closely correlated with aortic pulse wave velocity and the central and peripheral systolic augmentation indexes. The arterial pressure wave consists of a forward component generated by the heart and reflected waves returning to the heart from peripheral sites.<sup>21</sup> In elastic arteries the reflected waves coincide with diastole and raise diastolic pressure. With arterial stiffening, for instance, as a consequence of aging<sup>25</sup> or hypertension,<sup>26</sup> the reflected waves move faster, reach the central arteries during systole and cause an augmentation of systolic pressure, whereas diastolic pressure decreases.<sup>21</sup> We observed that AASI remained closely correlated with systolic augmentation after adjustment for major determinants of wave reflection, including body height and heart rate. When these factors are held constant, systolic augmentation is also a measure of arterial stiffness.<sup>27</sup> Moreover, the novel index closely correlated with central, as well as peripheral pulse pressure. Many researchers used pulse pressure as a measure of arterial stiffness.<sup>28,29</sup> However, pulse pressure only reflects the static difference between systolic and diastolic pressure and does not exploit the diurnal variability in the relation between the inflection points of the arterial pressure wave.

AASI was derived from 24-hour ambulatory blood pressure monitoring, which measures peripheral blood pressure at the brachial artery. Wave reflections are, therefore, likely to contribute to the variation in AASI. This might explain why AASI was higher in women than men and decreased with

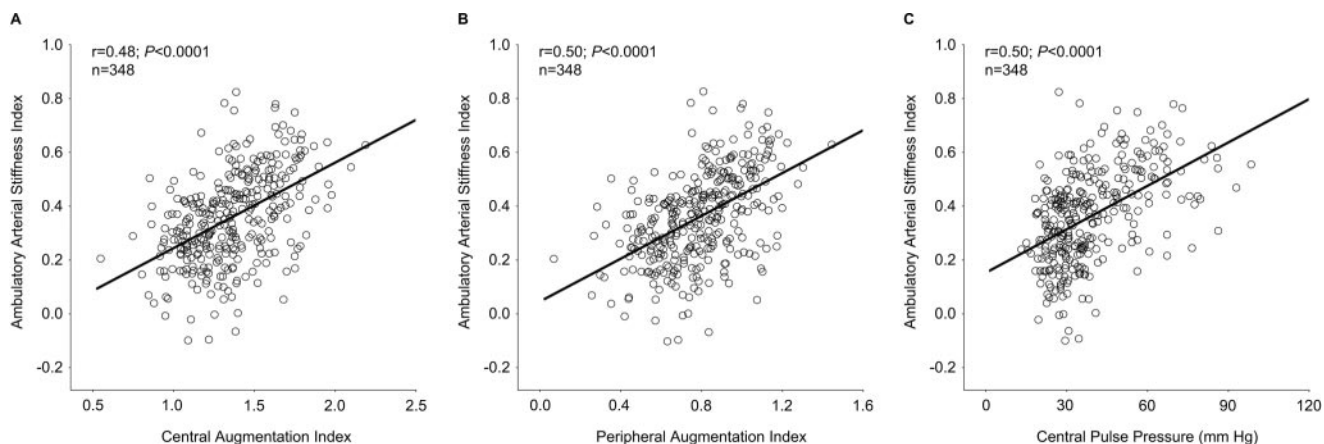


Figure 3. Correlations of the AASI with the central (A) and peripheral (B) augmentation indexes and central pulse pressure (C).

**TABLE 4. Correlations Between Indexes of Arterial Stiffness**

Dependent Variable	All Subjects		<40 Years		≥40 Years	
	AASI	PPP	AASI	PPP	AASI	PPP
Central augmentation index						
Unadjusted	0.48§#	0.34§	0.18†	-0.00	0.37§¶	0.27‡
Adjusted*	0.39§#	0.28§	0.17†	0.05	0.24‡	0.19‡
Peripheral augmentation index						
Unadjusted	0.50§#	0.36§	0.19†	-0.02	0.41§¶	0.33§
Adjusted*	0.41§#	0.30§	0.17†	0.03	0.30§	0.26‡

PPP indicates peripheral pulse pressure determined from the 24-hour ambulatory blood pressure recordings.

\*Adjusted for body height and 24-hour heart rate.

Significance of the correlation coefficients: † $P < 0.05$ ; ‡ $P < 0.01$ ; § $P < 0.0001$ .

Significance of the difference between correlation coefficients with AASI and PPP: || $P < 0.05$ ;

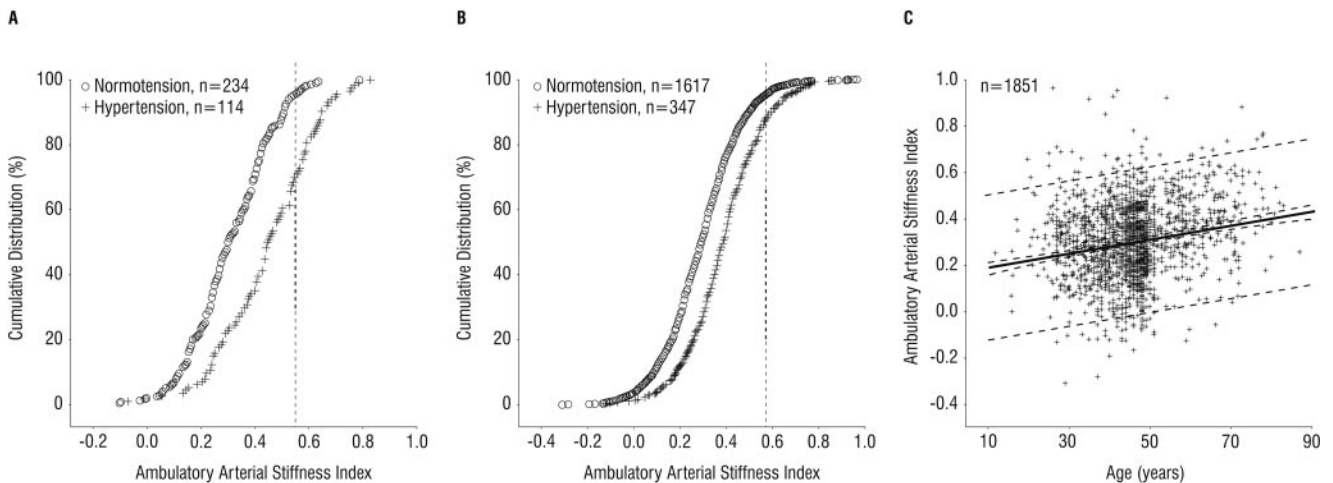
¶ $P < 0.01$ ; # $P < 0.0001$ .

body height. However, AASI was not correlated with heart rate. The computation of AASI was based on the diurnal variation in systolic and diastolic blood pressure within each subject. These changes reflect daily physical activity and psychoemotional stress, which also influence heart rate. Within participants, the 24-hour systolic and diastolic blood pressures correlated positively with the 24-hour heart rate. The correlation coefficients averaged  $\approx 0.30$  ( $P < 0.01$ ). The association between AASI and heart rate did not reach significance, probably because AASI also depends on the diurnal variation in each person's heart rate.

AASI, like aortic pulse wave velocity,<sup>25</sup> linearly increased with age in women and men, whereas the relation between pulse pressure and age is curvilinear.<sup>30</sup> Diastolic blood pressure rises with increased peripheral arterial resistance but falls with increased stiffness of the large conduit arteries.<sup>21</sup> In young compared with old adults, pulse pressure is mainly influenced by peripheral arterial resistance, and systolic augmentation at the level of the brachial arteries is less pronounced.<sup>21</sup> We observed that, at <40 years of age, AASI, but not pulse pressure, correlated with systolic augmentation.

Thus, compared with pulse pressure, AASI might be an indicator of arterial dysfunction at a much younger age.

AASI is continuously distributed in populations. However, for risk stratification and diagnosis, clinicians need operational thresholds to differentiate normality from pathologic conditions. For this reason, we studied the cumulative distribution of AASI in normotensive and hypertensive subjects. Among normotensive individuals, the 95th percentiles of AASI were highly consistent among Chinese and European subjects. For individual subjects, the upper boundary of the 95% prediction interval in relation to age ranged from 0.50 at 20 years to 0.70 at 80 years. However, definite validation of a new diagnostic index can only rely on its association with target organ damage and health outcomes in cross-sectional but preferably prospective studies. As reported in our companion article, based on 11 291 hypertensive patients enrolled in the Dublin Outcome Study and followed up for a median interval of 5.3 years, AASI predicted cardiovascular mortality over and beyond classical risk factors.<sup>8</sup> These findings might have implications for the interpretation of clinical trials in hypertension, in whom part of the benefit might be attributed



**Figure 4.** Cumulative distribution of the ambulatory arterial stiffness index in Chinese (A) and in Belgian and Irish (B) normotensive subjects (circles) and hypertensive patients (+). In A and B, the dotted lines represent the 95th percentile in normotensive subjects. C shows the regression line and the 95% prediction bands for mean and individual values of the AASI in relation to age in 1851 normotensive subjects of the 3 populations combined.

to a greater reduction in systolic blood pressure in the central than peripheral arteries.<sup>27,31</sup>

In conclusion, we identified a novel index of arterial stiffness, which can be easily measured under ambulatory conditions by means of regular devices for ambulatory monitoring of blood pressure. Pending additional validation in outcome studies, normal values of AASI are likely to be <0.50 at 20 years and 0.70 at 80 years.

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