Original Article

Ambulatory Arterial Stiffness Index or Pulse Pressure: Which Correlates Better with Arterial Stiffness in Resistant Hypertension?

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The ambulatory arterial stiffness index (AASI) is a recently proposed index derived from 24-h ambulatory blood pressure monitoring (ABPM) for the evaluation of arterial stiffness. In this cross-sectional study we investigated whether AASI reflects arterial stiffness in patients with resistant hypertension by comparing AASI and ambulatory pulse pressure (PP) with aortic pulse wave velocity (PWV), a measure of arterial stiffness, in 391 resistant hypertensives. Clinical, laboratory and echocardiographic variables, 24-h ABPM and aortic PWV (measured using the Complior device) were obtained. AASI was calculated as 1 – the regression slope of 24-h diastolic on systolic blood pressure (BP). Statistical analysis involved single and multiple linear regressions to assess the correlations between the two ABPM variables and PWV, both unadjusted and adjusted for potential confounders (age, gender, body height, presence of diabetes, 24-h mean arterial pressure [MAP], heart rate, and nocturnal BP reduction). Ambulatory PP and aortic PWV were independently associated with age, gender, presence of diabetes, and 24-h MAP, whereas AASI was associated with age, diabetes, and nocturnal diastolic BP reduction. PP showed stronger unadjusted (r=0.39, p<0.001) and adjusted (r=0.22, p<0.001) correlations with aortic PWV than AASI (r=0.12, p=0.032 and r=−0.04, p=0.47, respectively). In the analysis of subgroups stratified by gender, age, presence of atherosclerotic diseases and diabetes, dipping pattern, and ambulatory BP control, the superiority of PP over AASI was apparent in all subgroups. In conclusion, 24-h ambulatory PP was better correlated to arterial stiffness, as evaluated by aortic PWV, than the novel AASI, in patients with resistant hypertension. (*Hypertens Res* 2008; 31: 607–613)

***Key Words*: arterial stiffness, ambulatory blood pressure monitoring, pulse pressure, pulse wave velocity, resistant hypertension**

Introduction

Arterial stiffness is a well-known predictor of cardiovascular morbidity and mortality (*1*–*3*), but there are many barriers to its evaluation. A great variety of factors determine arterial stiffness, including the geometric (vessel diameter) and structural (wall composition) architecture of the vascular system (*4*), genetic and environmental factors, atherosclerotic diseases, diabetes, age, gender, and blood pressure (BP) levels (*4*, *5*). Because ventricular ejection and arterial stiffness are the main determinants of pulse pressure (PP), PP is often used as an indirect way to reflect arterial stiffness (*6*). Currently, pulse wave velocity (PWV) is a standard indicator of arterial

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stiffness (*4*, *5*), but its use is limited because highly expensive, complex equipment and trained personnel are required for its measurement, and sometimes there are difficulties in simultaneous measurements at different sites (*7*).

Recently, a new index derived from 24-h ambulatory BP monitoring (ABPM) recordings, ambulatory arterial stiffness index (AASI), was proposed to evaluate arterial stiffness (*8*). AASI is defined as 1 − the slope of the diastolic on systolic BP during ABPM. This index showed good correlation with PWV in normotensives and in mild untreated hypertensive patients (*8*). It was also demonstrated that it might be a marker of increased cardiovascular mortality over and above 24-h PP, particularly in young normotensive individuals (*9*). Nevertheless, there has been no study investigating the relationships between this new index and aortic PWV in patients with resistant hypertension (RH), a subgroup of hypertensives in whom the performance of ABPM is desirable (*10*). Thus, the aim of this study was to evaluate whether AASI is a better indicator of arterial stiffness than the conventional ambulatory PP in RH, by comparing the correlations of AASI and PP with aortic PWV (*11*).

Methods

Study Population and Baseline Procedures

A cross-sectional study involving 391 consecutive patients with RH enrolled between March 2006 and April 2007 was conducted at our hospital clinic. All participants gave written informed consent, and the study protocol conformed to the Declaration of Helsinki was approved by the local Ethics Committee. The characteristics of this cohort as well as the baseline procedures and the diagnostic definitions have already been detailed elsewhere (*10*, *12*, *13*). In brief, all hypertensive patients referred to our clinic who fulfilled the criteria for RH (office BP ≥140/90 mmHg using at least 3 antihypertensive drugs in full dosages, always including a diuretic) without peripheral arterial disease and secondary hypertension, were submitted to a standard protocol that included a thorough clinical examination, laboratory evaluation, 12-lead ECG, 2-dimensional (2D)-echocardiography, 24-h ABPM, and PWV measurement. Only patients considered at least moderately adherent to treatment were enrolled into the study (*12*). BP was measured twice, with patients in the sitting position, using a digital BP monitor, HEM-907 XL OMRON (*14*), with a suitably sized cuff. BP considered was the mean between the two readings. PP was calculated as systolic BP (SBP) − diastolic BP (DBP) and mean arterial pressure (MAP) as DBP+(PP/3) (*15*).

ABPM was carried out using an oscillometric device (Mobil O Graph, version 12; Numed, Sheffield, UK), approved by the British Hypertension Society (*16*). A reading was taken every 15 min throughout the day and every 30 min at night. All patients used their prescribed antihypertensive medications during ABPM. Parameters evaluated were mean 24-h, diurnal and nocturnal SBP, DBP, PP, MAP, and nocturnal SBP/DBP reduction. A non-dipping pattern was defined as a fall of <10% in both nocturnal SBP and DBP. Isolated non-dipping SBP was also analyzed. The nocturnal period was ascertained for each individual patient from registered diaries. After ABPM the patients were classified as having either true (uncontrolled) RH (daytime ABPM ≥135/85 mmHg) or white-coat (controlled) RH (daytime ABPM <135/85 mmHg) (*12*). In a previous analysis, 24-h (r=0.39) and nighttime PP (r=0.42) were the best crude correlates to aortic PWV among all traditional ABPM parameters. As the difference between these two variables was only slight and non-significant, we decided to use 24-h PP to increase the generalization and comparability of our results with previous reports. From individual 24-h recordings, we computed the regression slope of diastolic on systolic BP and calculated the AASI (1 − the coefficient of the regression slope). The regression method was standard asymmetrical linear regression and the slope was not forced through the origin, as originally described (*8*).

Immediately after the 24-h ABPM recording, a single,

Table 1. Baseline Characteristics of the Study Population

Characteristics (n=391)	
Female gender, %	71.4
Age, years	64.0±10.1
Height, cm	158±9
BMI, kg/m^2	29.4±5.2
Number of antihypertensive drugs	3.9±0.9
Diabetes, %	37.8
Dyslipidemia, %	68.3
CHD, %	23.5
Cerebrovascular disease, %	15.8
Atherosclerotic diseases,* %	36.3
LVMI, g/m^2	146±43
Office SBP, mmHg	162±30
Office DBP, mmHg	86±18
Office PP, mmHg	76±24
24 h SBP, mmHg	136±19
24 h DBP, mmHg	77±13
24 h PP, mmHg	59±13
Nocturnal SBP reduction, %	7.3±9.1
Nocturnal DBP reduction, %	9.1±10.1
Non-dipper SBP, %	64.9
Non-dipper SBP and DBP, %	68.3
AASI	0.55±0.14
Aortic PWV, m/s	10.8±2.3

*Atherosclerotic diseases: coronary heart disease and/or cerebrovascular disease. BMI, body mass index; CHD, coronary heart disease; LVMI, left ventricular mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; AASI, ambulatory arterial stiffness index; PWV, pulse wave velocity.

Table 2. Independent Correlates of Each Arterial Stiffness Parameter Estimated by Multiple Linear Regression

Covariates	Aortic PWV	AASI	24-h PP
Age (years)	0.49*	0.16†	0.46*
Gender (1, men; 2, women)	−0.13‡	0.08	0.26*
Diabetes (0, no; 1, yes)	0.31*	0.17†	0.17†
24-h MAP (mmHg)	0.24*	0.06	0.57*
Nocturnal DBP reduction (%)	−0.11‡	−0.21*	−0.12‡

Correlation coefficients are multivariate adjusted partial coefficients derived from linear regression. Significance of the correlation coefficients: *$p<0.001$; †$p<0.01$; ‡$p<0.05$. Candidate variables to enter the regression models were the following: age, gender, body height, presence of diabetes, dyslipidemia, coronary heart disease and cerebrovascular disease, 24-h MAP, nocturnal SBP and DBP reduction, 24-h mean heart rate, number of antihypertensive drugs in use, and the classes of antihypertensive drugs. PWV, pulse wave velocity; AASI, ambulatory arterial stiffness index; PP, pulse pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure.

Table 3. Correlations between ABPM Indexes of Arterial Stiffness and Aortic PWV in All Patients and in Stratified Subgroups by Gender and Older Age

Dependent variable: Aortic PWV	AASI	24-h PP
All patients ($n=391$)		
Unadjusted	0.12‡	0.39*,§
Adjusted[a]	−0.04	0.22*,§
Male ($n=112$)		
Unadjusted	0.13	0.42*,§
Adjusted[a]	−0.04	0.22‡,#
Female ($n=279$)		
Unadjusted	0.12	0.42*,§
Adjusted[a]	−0.04	0.21†,#
Age ≤60 years ($n=140$)		
Unadjusted	0.05	0.31*,§
Adjusted[a]	0.01	0.21‡,§
Age >60 years ($n=251$)		
Unadjusted	0.05	0.35*,§
Adjusted[a]	−0.07	0.15‡,#

Correlation coefficients are unadjusted single Pearson's coefficient and multivariate adjusted partial coefficients derived from linear regression. [a]Adjusted for age, gender, body height, 24-h mean arterial pressure and heart rate, diabetes, and nocturnal diastolic blood pressure reduction. Significance of the correlation coefficients: *$p<0.001$; †$p<0.01$; ‡$p<0.05$. Significance of the differences between AASI and PP correlation coefficients: §$p<0.01$; #$p<0.05$. ABPM, ambulatory blood pressure monitoring; PWV, pulse wave velocity; AASI, ambulatory arterial stiffness index; PP, pulse pressure.

trained independent observer unaware of other patients' data measured carotid-femoral PWV using the foot-to-foot velocity method with the Complior SP equipment and software (Artech-Medical, Paris, France), previously validated (*17*), and with the patients in a supine position. Briefly, waveforms were obtained transcutaneously over the right common carotid artery and the right femoral artery simultaneously during a minimum period of 10 to 15 s. The time delay (t) was measured between the feet of the 2 waveforms, and the distance (D) covered by the waves was measured directly between the femoral recording site and the supra-sternal notch minus the distance from the supra-sternal notch to the carotid recording site. PWV was calculated as D (m)/t (s). Three consecutive readings were obtained and the PWV was taken as the mean between them.

Statistical Analysis

Continuous data were described as the means±SD. Assessment of normal data distribution was investigated by Kolmogorov-Smirnov test. Variables independently associated with each arterial stiffness parameter (PWV, AASI, and 24-h PP) were evaluated by multiple linear regression. In multiple regression, a stepwise forward procedure was used to select the covariates (a p value <0.20 was necessary to enter and a p value <0.10 was required to remain in the models). Specifically, the influence of antihypertensive drug treatment on each arterial stiffness parameter was tested by forcing it into the multivariate models and also by including interaction terms between each arterial stiffness parameter and each antihypertensive drug class (diuretics could not be evaluated because all patients used them).

Correlations between AASI or PP and aortic PWV were analyzed by single (Pearson's coefficient of correlation) and multiple linear regression analysis to allow adjustment for potential confounders (age, gender, body height, presence of diabetes, 24-h MAP and heart rate, and nocturnal DBP reduction). The correlation coefficients of AASI and PP were compared by the z test for comparisons of r values. A stratified correlation analysis, both adjusted and non-adjusted, was also performed for older age (>60 years), gender, presence of atherosclerotic diseases and diabetes, dipper or non-dipper status, and controlled or uncontrolled BP on ABPM. All statistics were performed using an SPSS statistical package, version 13.0, and a two-tailed p value <0.05 was regarded as significant.

Results

A total of 391 resistant hypertensives were included in the study (71.4% females, mean age 64.0 years [SD: 10.1]). Patients used a median of 4 antihypertensive drugs: 100% were on diuretics, 96% on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 88% on β-block-

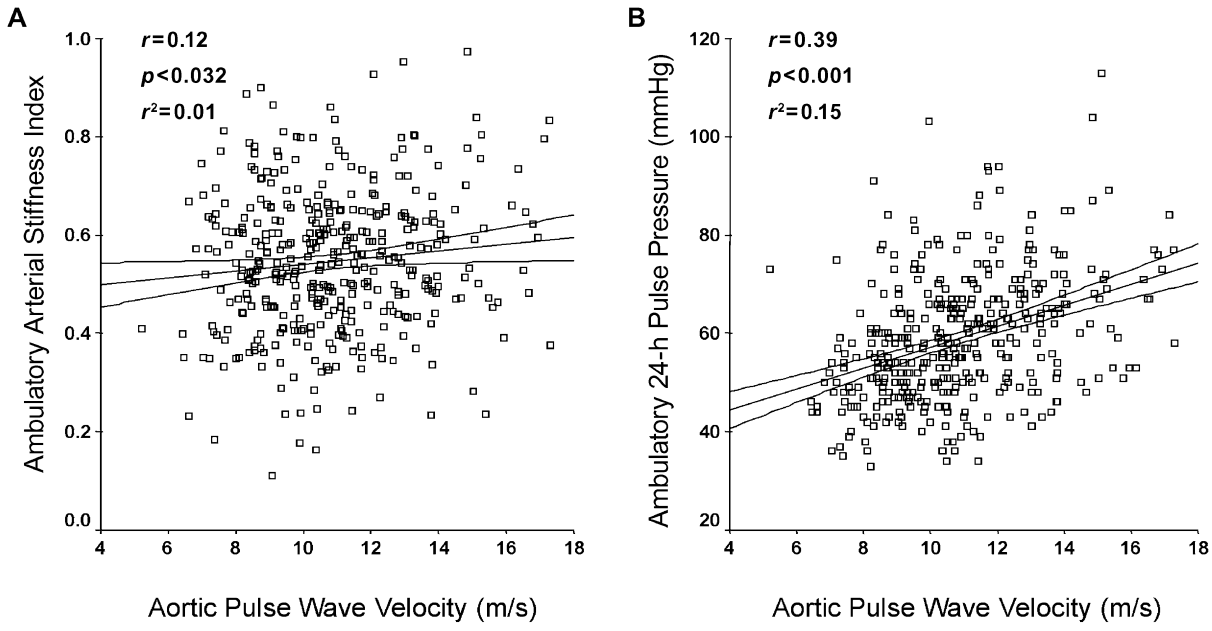

Fig. 1. *Correlations between aortic PWV and ambulatory arterial stiffness index (A) or 24-h ambulatory pulse pressure (B).*

ers, 73% on calcium channel blockers, 43% on direct vasodilators and 23% on centrally acting α-agonists. Table 1 shows the baseline characteristics of the study population. Aortic PWV averaged 10.84±2.30 m/s (range 5.20–17.30), AASI averaged 0.55±0.14 (range 0.11–0.97) and 24-h PP averaged 59±13 mmHg (range 33–113). All parameters were normally distributed (Komolgorov-Smirnov $p>0.10$).

Table 2 shows the variables independently associated with each arterial stiffness parameter. Aortic PWV and ambulatory PP shared the same correlates: age, gender, presence of diabetes, 24-h MAP and, to a lesser extent, the magnitude of nocturnal diastolic BP reduction. Nevertheless, gender had a differential effect: men had a lower PP (56±11 *vs.* 60±13 mmHg, $p=0.006$) but a higher PWV (11.3±2.4 *vs.* 10.6±2.2 m/s, $p=0.007$) than women. AASI was associated with age, diabetes, and most strongly with the magnitude of nocturnal DBP fall, but not with 24-h MAP or gender. No specific antihypertensive drug, nor the presence of any atherosclerotic vascular disease (coronary or cerebrovascular disease) independently affected any arterial stiffness parameter.

Table 3 shows the correlations between the ABPM indexes of arterial stiffness (AASI and 24-h PP) and aortic PWV in all patients and in subgroups stratified by gender and age. In all patients, the unadjusted single correlation coefficients were significantly higher for 24-h PP than for AASI, although the correlations between AASI and aortic PWV were also significant. After adjustment for potential confounders, only PP remained significantly associated with aortic PWV. Discarding outliers from AASI calculation and correlation analyses did not alter the results. Adjusting for dipping or non-dipping status (either evaluated as nocturnal SBP and DBP fall or only as SBP fall) instead of adjusting for continuous nocturnal DBP fall, also had no effect on the results. Figure 1 shows the scatter plots between each proposed ABPM index of arterial stiffness and aortic PWV. The superiority of PP over AASI as a correlate to aortic PWV was evident both in men and women and in older (>60 years) and younger individuals.

Table 4 presents the correlation analysis for other subgroups stratified by the presence of atherosclerotic diseases (coronary or cerebrovascular), diabetes, dipping pattern, and BP control on ABPM (white-coat or true RH). PP correlated more closely with aortic PWV than AASI in all subgroups, even after adjustment for potential confounding variables. Using only nocturnal SBP fall to define the non-dipping pattern, instead of both SBP and DBP reduction, had no effect on the results.

Discussion

The present study provides the first investigation of the relationships between the recently proposed AASI and aortic PWV in patients with RH. The main finding of our study is that 24-h ambulatory PP was better correlated to arterial stiffness, as estimated by aortic PWV, than the AASI in RH patients, independent of gender, age, body height, presence of diabetes, 24-h MAP and heart rate, and magnitude of nocturnal BP reduction.

RH patients are characteristically older subjects, with greater prevalences of atherosclerotic risk factors and target-organ damage (*10*, *12*, *18*) due to their long-term exposure to high BP levels (*19*). So, it is expected that they would show increased arterial stiffness. Moreover, the performance of

Table 4. Correlations between ABPM Indexes of Arterial Stiffness and Aortic PWV in Patients Stratified by the Presence of Atherosclerotic Diseases (Coronary or Cerebrovascular), Diabetes, Dipping Pattern and Hypertension Control on ABPM

Dependent variable: Aortic PWV	AASI	24-h PP
Atherosclerotic diseases present (n=142)		
Unadjusted	0.05	0.39*,§
Adjusted[a]	−0.11	0.26†,§
Atherosclerotic diseases absent (n=249)		
Unadjusted	0.14‡	0.38*,§
Adjusted[a]	0.01	0.19†,#
Diabetes (n=148)		
Unadjusted	0.15	0.39*,§
Adjusted[a]	0.01	0.22†,#
Non-diabetes (n=243)		
Unadjusted	0.01	0.35*,§
Adjusted[a]	−0.08	0.20†,§
Dipper (n=124)		
Unadjusted	−0.01	0.26†,#
Adjusted[a]	−0.14	0.12
Non-dipper (n=267)		
Unadjusted	0.13‡	0.45*,#
Adjusted[a]	0.01	0.27*,§
WC-RH (n=149)		
Unadjusted	−0.02	0.21‡,#
Adjusted[a]	−0.09	0.20‡,#
True RH (n=242)		
Unadjusted	0.15‡	0.41*,#
Adjusted[a]	−0.05	0.24*,§

Correlation coefficients are unadjusted single Pearson's coefficient and multivariate adjusted partial coefficients derived from linear regression. [a]Adjusted for age, gender, body height, 24-h mean blood pressure and heart rate, diabetes, and nocturnal diastolic blood pressure reduction. Significance of the correlation coefficients: *$p<0.001$; †$p<0.01$; ‡$p<0.05$. Significance of the differences between AASI and PP correlation coefficients: §$p<0.01$; #$p<0.05$. ABPM, ambulatory blood pressure monitoring; PWV, pulse wave velocity; AASI, ambulatory arterial stiffness index; PP, pulse pressure; WC-RH, white-coat resistant hypertension; RH, resistant hypertension.

ABPM is obligatory in RH patients, both to guide therapy and prognosis (*20*, *21*). Thus, the investigation of an ABPM-derived index that could reflect increased arterial stiffness in this subgroup of hypertensives is particularly important to improve cardiovascular risk stratification.

AASI is a recently proposed index (*8*) to evaluate arterial stiffness using ABPM measurements. It was shown in 166 normotensive Chinese volunteers and in 348 Chinese individuals randomly recruited from communities, most of them normotensives or mild hypertensives (only 14% on antihypertensive drug treatment), that AASI correlated better with aortic PWV and systolic augmentation index than ambulatory PP, in both non-adjusted and adjusted analyses (*8*). Nevertheless, only adjustments for body height and 24-h heart rate were performed, and no allowance was made for age, gender or mean 24-h BP.

These investigators further demonstrated in a companion paper (*9*) that AASI was a better predictive marker for cardiovascular mortality than ambulatory PP, particularly for fatal stroke and in young normotensive or well-controlled hypertensive individuals. Indeed, when both AASI and PP were included in the multivariate survival analyses as continuous variables, AASI predicted fatal stroke, whereas PP was a better predictor of cardiac death. A recent report of a population-based study (*22*) confirmed the prognostic value of AASI for incident strokes, especially in normotensive individuals. In two other recently reported studies in untreated, mainly mild hypertensive patients (*23*, *24*), strong relationships between AASI and target-organ damage and renal damage were demonstrated, as previously observed for PP (*25*).

Contrary to the original report of the AASI (*8*), our study demonstrated that in RH patients, ambulatory PP was better correlated to aortic PWV than AASI. The superiority of PP over AASI, as a correlate to aortic PWV, was evident in both genders, in older and younger individuals (Table 3), in patients with and without atherosclerotic diseases, in diabetic and non-diabetic subjects, in dippers and non-dippers, and in white-coat (controlled BP) and true (uncontrolled) RH patients (Table 4). These differences persisted or increased after adjustment for several potential confounders, including 24-h MAP, nocturnal DBP reduction, diabetes, age, and gender. AASI was significantly, but weakly, associated with aortic PWV only in patients without atherosclerotic diseases, in non-dippers and in true RH patients, although these associations became non-significant after further adjustment for confounders. Ambulatory 24-h PP, on the other hand, remained significantly associated with aortic PWV after adjustment in all subgroups, except in dipper individuals.

These conflicting findings might be related to the different populations of patients evaluated. That is, our patients were older and had higher office and ambulatory BP levels. Also, the influence of antihypertensive drug treatment on arterial stiffness parameters (*26*) can not be ruled out, although we did not detect any significant interaction between any specific antihypertensive drug or therapeutic regimen and any arterial stiffness parameter in our multivariate analyses.

Aortic PWV, one of the standard measurements of arterial stiffness, is mainly determined by age and BP levels (*27*, *28*). In the present analysis, it was additionally associated with gender (being slightly higher in men) and with the presence of diabetes. In the original report (*8*), the AASI was independently associated with age, MAP, and body height, and borderline associated with gender (higher in women), whereas in our study it was associated with age, diabetes, and magnitude

of nocturnal DBP reduction (higher in non-dippers), but not with gender or MAP. Ambulatory 24-h PP shared the same independent correlates of PWV, although with an opposite effect of gender (higher in men). Even though gender may affect arterial stiffness by differences in arterial wall composition and in vessel size and length (*4*), unlike the systolic augmentation index, the effect of gender on aortic PWV is considered to be small (*27*). In general, women tend to have shorter vessels, higher PP and central systolic augmentation (*27*), and a greater prevalence of systolic hypertension, which usually become more prominent after menopause (*4*). Our study corroborated these tendencies.

A recently reported study (*29*) in which 346 untreated hypertensives were evaluated by aortic PWV and ABPM strongly supports our findings. The authors showed a significant association ($r=0.28$) between AASI and aortic PWV that disappeared completely after adjustment for other independent correlates (age, heart rate, MAP, and metabolic syndrome) of aortic PWV. Furthermore, in agreement with our findings, they demonstrated that AASI was mainly determined by the magnitude of nocturnal BP reduction. This occurs because of the mathematical dependence of the regression slope on the range variation of the 24-h DBP; the greater the variation of 24-h DBP (as in dipping subjects), the higher the expected regression slope and the lower its reciprocal, the AASI. The opposite occurs in non-dipping individuals. In another report, a prospective study (*30*) that evaluated 1,043 elderly diabetic patients with a mean follow-up of 30 months, the authors concluded that 24-h PP was superior to AASI in predicting the progression of albuminuria.

Clearly, the finding of a close correlation between two parameters (PWV and PP or AASI) does not imply that there is only a single link between them (*31*). 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, increasing aortic and peripheral PP (*32*). The exact physiopathological meaning of the AASI in terms of arterial regulation is still not established. Recently, it was suggested that the AASI may be a measure of ventriculo-arterial coupling because, from a mathematical perspective, it depends on arterial factors (arterial compliance and vascular resistance) and on cardiac factors (stroke volume and heart rate) (*33*). Even though many authors (*8*, *9*, *22*, *23*) consider both ambulatory PP and AASI surrogates of arterial stiffness, these parameters probably have different physiological meanings than the arterial stiffness itself (*31*) and should be considered at best as surrogates of other direct measures of arterial stiffness, such as aortic PWV. Our findings indicate that, in RH patients, 24-h PP is a better ABPM-derived surrogate marker of arterial stiffness than the new AASI, although the strength of the correlation between them is only moderate.

Some limitations of this study are important to note. First, as the RH population is characteristically older, our study group included only a small number of patients younger than 50 years. So, the relationships demonstrated here between ABPM indexes of arterial stiffness and aortic PWV may not be directly extensible to patients in these lower strata of age, and must be confirmed by other studies with a greater number of young RH patients. Moreover, our results can not be generalized to other less severe or well-controlled hypertensive patients, especially because of the great number of antihypertensive drugs that could affect PWV and AASI calculation, although we did not find any significant difference between specific antihypertensive drugs or combinations of drugs. It is also important to note that the cross-sectional design of the present study imposed several limitations. For instance, no cause-effect relationship between ABPM indexes, arterial stiffness and target-organ damage could be inferred. Thus, adequately powered prospective studies are necessary to verify not only whether arterial stiffness precedes target-organ damage and cardiovascular morbi-mortality, but also which arterial stiffness marker best reflects these earlier alterations on vessel wall composition and distensibility. Moreover, we evaluated brachial PP, which can be influenced by other factors such as heart rate, cardiac contractility, venous pressure and the amplification phenomenon. Central aortic PP has recently been demonstrated to be more important than peripheral brachial PP in the management of hypertension (*34*).

In conclusion, this study provides evidence that, in resistant hypertensives, a subgroup of patients that particularly benefits from ABPM, ambulatory 24-h PP is better correlated to arterial stiffness, measured by aortic PWV, than AASI. Future studies are necessary to determine which of AASI or ambulatory PP is more useful for stratification of other cardiovascular risk factors in resistant hypertension, as well as to determine an optimal approach for this group of severely hypertensive patients.

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