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Factors Associated with Increased Radial Augmentation Index in Hypertensive Individuals

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Abstract

Background: Arterial stiffness is a variable predictor of morbidity and mortality and a possible marker of vascular injury. Its non-invasive assessment by radial tonometry and analysis of the augmentation index (r-AI) allows identifying patients exposed to higher cardiovascular risk.

Objective: To analyze the influence of r-AI on clinical-biochemical variables and its influence on the prevalence of target-organ damage in hypertensive patients.

Methods: 140 consecutive hypertensive patients, followed-up in an outpatient clinic, were analyzed in a cross-sectional study. Blood pressure (BP) levels and r-AI were obtained by applanation tonometry of the radial artery (HEM-9000AI, Onrom). The patients were allocated into r-AI tertiles (r-AI $\leq$ 85%; 85 < r-AI $\leq$ 97%; r-AI > 97%).

Results: The sample was predominantly composed of women (56.4%), mean age of 61.7 ± 11.7 years and body mass index 29.6 ± 6.1 Kg/m². The highest tertile showed higher proportion of women (p = 0.001), higher systolic BP (p = 0.001) and pulse pressure (p = 0.014), and lower weight (p = 0.044), height (p < 0.001) and heart rate (p < 0.001). Multivariate analysis demonstrated that weight (β = -0.001, p = 0.017), heart rate (β = -0.001, p = 0.007) and central pressure (β = 0.015, p < 0.001) correlated independently with r-AI. In logistic regression analyses, the 3rd r-AI tertile was associated to lower levels of diabetes (DM) (OR = 0.41; 95% CI 0.17-0.97; p = 0.042).

Conclusions: This study demonstrated that weight. heart rate and central BP were independently related to r-AI. (Arq Bras Cardiol 2011; 97(3) : 241-248)

Keywords: Arteries / physiopathology; blood pressure; elasticity; hypertension; coronary artery disease.

Introduction

Since the publication of the Conduit Artery Function Evaluation (CAFE) study[1], the importance of assessment of arterial function and central blood pressure increased substantially. Despite the fact that brachial blood pressure is a powerful predictor of cardiovascular morbidity and mortality[2], these measurements do not reflect the pressure in the central circulation. Recent evidence showed that central blood pressure is more relevant to cardiovascular outcomes than pressures in the brachial artery[1,3,4].

It is well recognized that arterial stiffness parameters predict clinical outcomes, such as coronary artery disease[5,6], stroke[6], urinary albumin excretion[7,8], progression of chronic kidney disease[9], survival in end-stage renal disease[10] and general cardiovascular risk[11]. The current standard for assessing this condition involves the measurement of several variables by noninvasive applanation tonometry, including the radial augmentation index (r-AI)[12]. r-AI, which is defined as an increase in pressure from the first systolic shoulder to the peak pressure of the aortic pressure waveform expressed as a percentage of peak pressure, has been correlated with left ventricular hypertrophy (LVH)[13], coronary artery disease[5], urinary albumin excretion[14], cardiovascular events[15,16] and all-cause mortality16, representing an easier and quicker method to access the central pressure[17,18].

Despite the fact that some variables such as age[19,20], height[11,18,20], heart rate[11,19,21-24], gender[11,18,19,21], systolic (SBP)20 and diastolic blood pressure (DBP)[11,19,20] have been correlated with the augmentation index, this relationship needs to be better established. Therefore, this study aimed to analyze the influence of r-AI on the prevalence of target-organ damage and to correlate this measure of arterial stiffness with clinical and biochemical variables in Brazilian hypertensive patients.

Methods

Subjects

A total of 140 consecutive hypertensive patients, aged $\geq$ 18 years, followed-up in an outpatient clinic from August/2009 to January/2010, were analyzed in a cross-sectional study. The study was previously approved by the Research Ethics Committee of the institution and all participants signed an informed consent. Individuals were allocated to three groups according r-AI tertiles: Group 1 (r-AI $\leq$ 85%) – 44 patients; Group 2 (85 < r-AI $\leq$ 97%) – 47 patients; Group 3 (r-AI > 97%) – 49 patients. The exclusion criteria were: history of atrial fibrillation or frequent supra- or ventricular premature beats for which accurate radial waveforms could not be obtained by the system, age $\geq$ 70 years and secondary hypertension.

Biochemical analysis, demographic data and target-organ damage

Peripheral blood was drawn in fasting for biochemical analysis of serum creatinine, total cholesterol, HDL-cholesterol, triglycerides and glucose. LDL-cholesterol was calculated by the Friedewald formula. Urinary albumin excretion (UAE) was determined by 24-h urine sample, considering normoalbuminuria as UAE < 20 μg/min, microalbuminuria as UAE between 20 and 200 μg/min and macroalbuminuria as UAE $\geq$ 200 μg/min.

For the assessment of comorbidities, data regarding the presence of diabetes mellitus, medications in usage, body mass index [BMI = weight (kg) / height (cm)^2], gender and other risk factors or necessary information were obtained from the medical record. Patients with diabetes mellitus (DM) were considered to be those who had been previously on hypoglycemic treatment or having fasting glucose levels $\geq$ 126 mg/dL on at least two occasions.

The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated MDRD (Modification on Diet in Renal Disease) formula. Renal failure was defined as eGFR $\leq$ 60 mL/min. LVH was determined by echocardiography, the normal left ventricular mass index (LVMI) for men was < 103 g/m^2 and for women < 89 g/m^2, as suggested by the American Society of Echocardiography[25].

Pulse wave and blood pressure analysis

Arterial pulse waveforms of the left radial artery were measured non-invasively by an automated tonometric system (HEM-9000AI; Omron Healthcare Co., Ltd., Kyoto, Japan) after 10 min of rest in a sitting position[12]. Pulse wave analyses were performed at least three times and the mean of measurements was analyzed. Radial arterial waveforms from this device, the first (P1) and late (second) systolic peaks (P2) were automatically identified using the fourth derivative wave as the second and third zero crossing points, respectively. Augmentation index (AI) was defined as the ratio of the height of P2 to that of P1. Brachial blood pressure (BP) and heart rate were measured simultaneously in the right brachium with an oscillometric

device incorporated into the HEM-9000 AI. Late systolic BP in the radial artery (rSBP2), as an index of central BP[26], was calculated by the following equation: rSBP2 = r-AI $\times$ (SBP−DBP) + DBP, in which SBP and DBP are brachial systolic and diastolic BP, respectively. All measurements were performed after at least 8-h fasting.

Statistical analysis

The calculated size of the sample, admitting a deviation of 1% to reject the hypothesis of nullity, was 122 patients. Previous studies exploring similar issues[7,21] analyzed a sample size similar to this study. Descriptive analysis was performed for qualitative variables and quantitative results are presented as mean $\pm$ standard deviations. To compare the characteristics of patients ANOVA for quantitative and χ2 for qualitative variables were used. Univariate and multivariate analyses were performed to assess the determinants of r-AI using various clinical variables. The variables that were statistically significant (p < 0.05) in the univariate analysis were then evaluated in the multivariate analysis. All statistical analyses were performed using the Minitab 16.0 statistical software. For all tests, a p value < 0.05 was considered significant.

Results

Table 1 shows the clinical and biochemical characteristics of the patients according to the tertiles of r-AI. There was an increase in the proportion of women into the highest tertile, with increasing levels of SBP and pulse pressure. In contrast, there was a progressive reduction in weight, height and heart rate with increasing r-AI, with no significant differences for biochemical and echocardiographic parameters. There were no differences in the history of diabetes, renal failure, LVH or alterations in urinary albumin excretion among tertiles (Table 2), with the exception of a higher prevalence of LVH in the 3rd tertile of r-AI in relation to the 2nd tertile (p = 0.026).

Using logistic regression analyses (Table 3), the third tertile of r-AI were associated with lower risk of diabetes mellitus (OR = 0.41; 95% CI 0.17-0.97; p = 0.042). There was no statistical significance (p > 0.05) for LVH and renal failure in the logistic regression.

Univariate (Table 4) and multivariate (Table 5) analyses were performed to assess factors determining r-AI. Univariate analysis showed that weight, height, gender, SBP, DBP, heart rate, pulse pressure, rSBP2 and glucose significantly correlated with r-AI. However, multivariate analysis demonstrated that only weight, heart rate and rSBP2 remained independently correlated with r-AI. Figures 1 and 2 show the relationship between r-AI with the variables that showed significance in the univariate analysis.

Discussion

In this study, we analyzed factors related to r-AI in a sample of hypertensive patients. The measure of arterial compliance through radial artery tonometry is a simple and easier method to assess arterial stiffness[17,18]. AI is strongly correlated with a previously validated estimate of arterial stiffness, pulse wave velocity (PWV)[12,18]. Its use to assess cardiovascular risk and drug effectiveness, as recently reported in the CAFE study,

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gives additional data for the stratification of cardiovascular risk and allows clinicians to customize antihypertensive therapies specifically to a single patient[1,2,17].

Recent reports show that AI is closely related with cardiovascular risk[11,16]. London et al[16] found that the risk ratio for each 10% increase in AI was 1.51 (95% CI 1.23-1.86) for all-cause mortality and 1.48 (95% CI 1.16-1.90) for cardiovascular mortality in a sample of end-stage renal failure patients. Nürnberger et al[11], on the other hand, found that AI significantly increased with increasing risk scores for cardiovascular disease.

Some studies have shown values that could be considered normal for AI using limits of normality based on the 95% confidence interval. Wojciechowska et al[26] in a European sample, proposed the value for peripheral AI of 90% for men and 100% for women. Shiburi et al[27] in a study which included black South Africans, proposed the thresholds to diagnose increased arterial

stiffness the value at age 30 years of 100% for peripheral AI, with adjustment by 10% for each decade that age differs from 30 years. Li et al[28] in a sample of 924 Chinese patients without cardiovascular disease demonstrated the approximate values for normal peripheral AI of 105% in a 40-year-old patient. Finally, Chung et al[29] demonstrated in a Korean sample that peripheral AI of 100% may be the preliminary reference values. Despite these data, the estimation of reference values for peripheral AI in this Brazilian sample was not possible due to be a hypertensive sample with multiple comorbidities, which would prevent the validation of such data.

According to previous studies, r-AI was significantly related to weight, height[11,18], gender[11,18,19,21,28-30], heart rate[11,19,21-23], SBP[23,30] and DBP[11,19], pulse pressure and glucose levels in univariate analyses. In this study, this association remained significant only for weight, height and heart rate in multivariate analyses. Body composition affects the timing of

Table 1 – Comparison between clinical and biochemical variables among the tertiles of augmentation index

Variable	All (n=140)	1st Tertile (n=44)[a]	2nd Tertile (n=47)[b]	3rd Tertile (n=49)[c]	p value* (axbxc)
Age (years)	61.7 ± 11.7	60.4 ± 10.6	61.0 ± 12.4	63.5 ± 12.0	NS
Gender (Male/Female)	61/79	27/17†	23/24‡	11/38	0.001
Weight (Kg)	78.4 ± 17.8	83.4 ± 21.7†	78.0 ± 15.4	74.3 ± 15.1	0.044
Height (m)	1.62 ± 0.09	1.66 ± 0.09†	1.63 ± 0.09‡	1.59 ± 0.06	<0.001
Body mass index (Kg/m2)	29.6 ± 6.1	30.2 ± 7.3	29.4 ± 5.2	29.4 ± 5.9	NS
eGFR (ml/min)	55.9 ± 15.8	56.2 ± 16.5	55.8 ± 12.0	55.6 ± 18.5	NS
Diabetes (%)	47.3	56.8†	50.0	34.9	NS
Biochemical parameters					
Glucose (mg/dL)	116.5 ± 49.9	129.9 ± 66.6	114.5 ± 41.1	106.4 ± 36.9	NS
HDL-cholesterol (mg/dL)	53.9 ± 13.8	56.1 ± 15.7	52.0 ± 14.7	53.9 ± 10.7	NS
LDL-cholesterol (mg/dL)	102.1 ± 34.5	102.0 ± 32.3	100.3 ± 37.3	104.0 ± 33.9	NS
Total cholesterol (mg/dL)	184.3 ± 46.6	185.9 ± 41.7	183.1 ± 56.4	183.2 ± 40.8	NS
Triglycerides (mg/dL)	136.9 ± 90.0	139.3 ± 65.1	146.4 ± 132.0	124.9 ± 49.9	NS
Creatinine (mg/dL)	1.4 ± 1.0	1.4 ± 0.4	1.3 ± 0.3	1.5 ± 1.6	NS
Urinary albumin excretion (µg/min)	110.6± 389.1	191.5 ± 630.1	72.2 ± 174.1	71.8 ± 191.1	NS
Tonometric parameters					
SBP (mmHg)	131.9 ± 21.8	123.2 ± 17.0†	130.3 ± 20.6‡	140.8 ± 23.6	0.001
DBP (mmHg)	73.4 ± 15.1	70.0 ± 11.2†	73.2 ± 16.0	77.4 ± 16.3	NS
Pulse pressure (mmHg)	58.2 ± 16.2	53.3 ± 12.1†	57.1 ± 16.5	63.4 ± 17.7	0.014
Heart rate (beats/min)	70.6 ± 13.7	77.7 ± 15.2†§	67.4 ± 12.9	67.7 ± 11.0	<0.001
r-AI (%)	91.7 ± 13.3	76.3 ± 7.5§	92.1 ± 3.4‡	105.4 ± 7.2	<0.001
rSBP1 (mmHg)	129.9 ± 20.9	123.7 ±16.9†	129.1 ± 20.6	136.0 ± 23.0	0.026
rSBP2 (mmHg)	125.0 ± 20.9	110.3±15.0†§	123.9± 20.1‡	138.4 ± 23.2	<0.001
Echocardiographic parameters					
Left ventricular mass (g)	216.0 ± 79.9	218.5 ± 87.5	213.8 ± 77.6	216.9 ± 77.3	NS
Left ventricular mass index (g/m2)	117.3 ± 40.7	112.8 ± 50.0	111.8 ± 39.2	123.5 ± 37.2	NS

Values are expressed as numbers with the percentages in parentheses or mean ± SD. NS – Not significant (p>0.05); eGFR – estimated glomerular filtration rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; r-AI – radial augmentation index; rSBP1 - First systolic BP in the radial artery; rSBP2 – Late systolic BP in the radial artery (central pressure); (*) ANOVA test; (†) 1st vs. 3rd tertile. p<0.05; (‡) 2nd vs. 3rd tertile. p<0.05; (§) 1st vs. 2nd tertile. p<0.05.

arterial wave reflection, explaining the correlation between r-AI and weight and height[31]. Gatzka et al[32] studied pairs of older men and women matched by age, BMI, and BP levels, and found that women had stiffer elastic arteries, suggesting an effect of female hormonal status in this relationship[31].

Other factors previously related to AI levels, such as age[19,29,30], BMI[30], creatinine clearance[30], hiperlipidemia[29,30] and LVMI[21] were not associated with r-AI levels in this sample. Aging is associated with histological changes in walls of systemic arteries, mainly in the intima and the in the media. These structural changes in the elastic arteries cause

an increase in both stiffness and resistance[31], explaining the relationship between AI and age.

There was no association between tertiles of r-AI and prevalence of the target-organ damage analyzed (renal failure, LVH and micro/macroalbuminuria). Despite this, there are reports that AI was associated with coronary artery disease[5], urinary albumin excretion[14] and LVH[13], suggesting a relationship between AI and target-organ damage. In relation to LVH, we found a high prevalence in this sample possibly due to the cutoff point adopted by the American Society of Echocardiography for its diagnosis[25]. The attenuation of the

Table 2 – Prevalence of target-organ damage according to tertiles of augmentation index

Variable	1st Tertile (n=44)[a]	2nd Tertile (n=47)[b]	3rd Tertile (n=49)[c]	p value* (axbxc)
Renal dysfunction (%)	57.1	64.4	57.8	NS
Left ventricular hypertrophy (%)	69.7	66.7†	87.8†	NS
Urinary albumin excretion				
Normoalbuminuria (%)	42.9	61.9	56.8	
Microalbuminuria (%)	40.5	26.2	36.4	NS
Macroalbuminuria (%)	16.7	11.9	6.8	

NS – Not significant (p > 0.05); (*) χ2 test; (†) 2nd vs. 3rd tertile, p = 0.026.
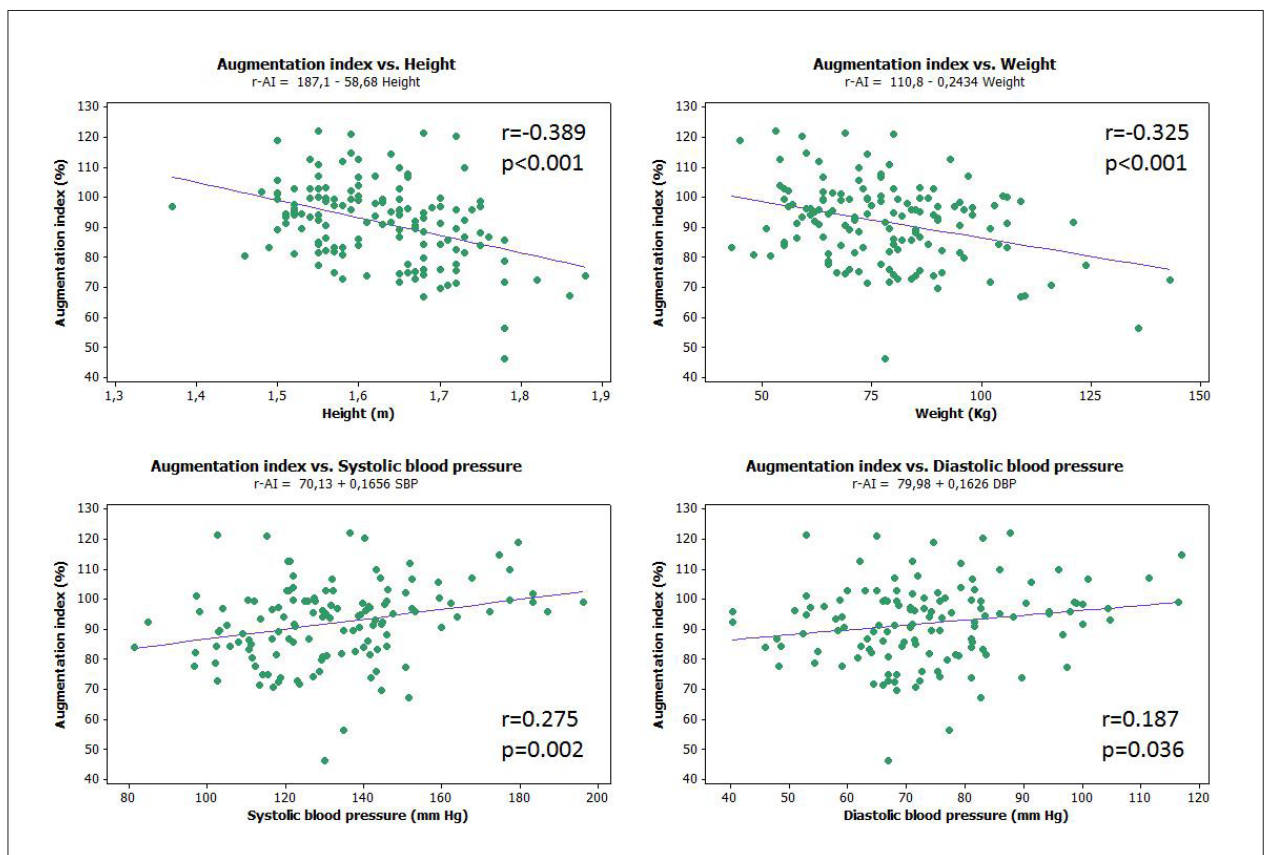
Figure 1 – Relationship between radial augmentation index with height. weight. systolic and diastolic blood pressure.

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cushioning of elastic arteries amplifies the pressure pulsatility and increases the transmission of pulsatile energy to the peripheral microcirculation[33]. This occurs particularly in high-blood flow organs, such as brain and kidney, where pressure pulsatility penetrates further into the microcirculation, causing damage to these organs[33,34].
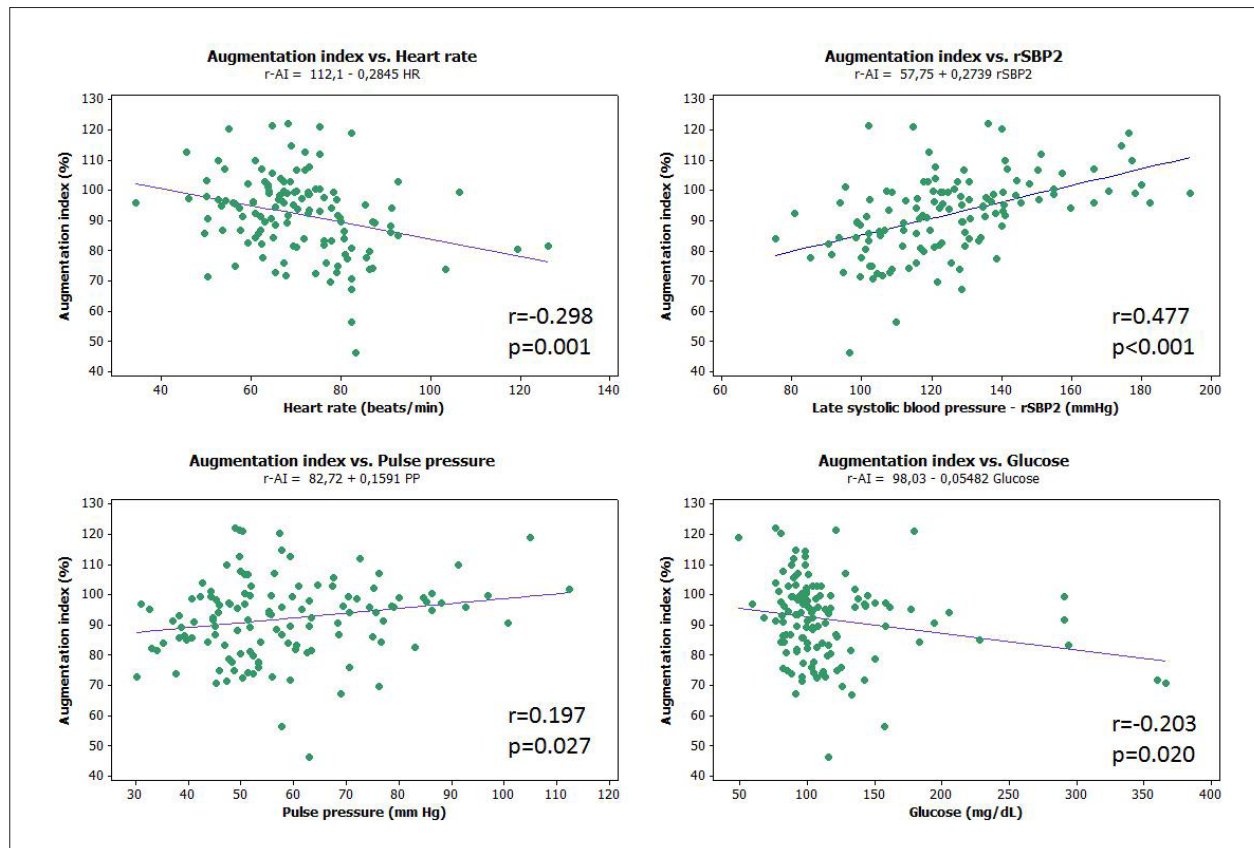

Figure 2 – *Relationship between radial augmentation index with heart rate. pulse pressure and glucose levels.*

Table 3 – Logistic regression analyses for diabetes and target-organ damages and tertiles of augmentation index

Variable	β	SE	Odds ratio (95% CI)	Valor p
Diabetes mellitus				
1st Tertile	-	-	1.00	-
2nd Tertile	-0.274	0.428	0.76 (0.33-1.76)	NS
3rd Tertile	-0.898	0.441	0.41 (0.17-0.97)	0.042
Left ventricular hypertrophy				
1st Tertile	-	-	1.00	-
2nd Tertile	-0.139	0.518	0.87 (0.31-2.40)	NS
3rd Tertile	1.411	0.609	3.13 (0.95-10.33)	NS
Renal dysfunction				
1st Tertile	-	-	1.00	-
2nd Tertile	0.307	0.440	1.36 (0.57-3.22)	NS
3rd Tertile	0.025	0.433	1.03 (0.44-2.40)	NS

NS – Not significant (p > 0.05).

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In relation to glucose metabolism status, we found an inverse relation between glucose levels and r-AI in the univariate analysis. However, when multivariate analyses are performed, this relationship is not present. Further, in the logistic regression, the 3rd tertile of r-AI was associated with lower prevalence of DM (OR = 0.41, 95% CI 0.17-0.97, p = 0.042). Studies of the association between type 2 DM and AI are inconclusive. Similarly to our results, Tomita et al[35] found in a sample of type 2 diabetic patients a negative association of r-AI to plasma glucose and HbA1c. Lacy et al[36] in a multiple regression analysis revealed that DM is a significant determinant of PWV, but not of AI. Guiadoni et al[37] also did not found any difference for AI between normotensive patients with and without metabolic syndrome. This same trend was observed by Wilhelm et al in a comparison between type 2 DM and controls[38]. On the other hand, Wilkinson et al[39] showed that AI was significantly high in diabetic patients compared with controls matched by sex, age, weight and height. Despite the fact that there was no difference

for AI between patients with impaired glucose metabolism and normoglicemic controls, Schram et al[40] found a higher aortic AI in patients with DM compared to normoglicemic controls. However, our study cannot provide evidence for these mechanisms. The relationship between r-AI and lower prevalence of DM may have simply coexisted.

This study has some limitations that deserve to be mentioned. Firstly, its cross-sectional design and relative small number of patients does not allow the investigation of the relationship between AI and primary outcomes (stroke and myocardial infarction). Secondly, the AI could have been influenced by heart rate. Therefore, although we did not adjust AI for heart rate, we measured it after 10 minutes of rest. Thirdly, due the fact of our service is a specialized outpatient clinic, we could not assess patients with newly diagnosed hypertension and without antihypertensive treatment for this study.

In conclusion, in our country, this is one of the pioneering studies evaluating the importance of central BP and markers of arterial stiffness (r-AI) in Brazilian hypertensive individuals. In this sample, weight, heart rate and central BP were independently related to r-AI.

Table 4 – Correlation coefficients of augmentation index with clinical-biochemical variables

Variable	r	p value
Age (years)	0.116	NS
Weight (Kg)	-0.325	< 0.001
Height (m)	-0.389	< 0.001
Gender (female)	0.343	< 0.001
Body mass index (Kg/m²)	-0.143	NS
SBP (mm Hg)	0.275	0.002
DBP (mm Hg)	0.187	0.036
HR (beats/min)	-0.298	0.001
rSBP2 (mmHg)	0.477	< 0.001
PP (mm Hg)	0.197	0.027
Total cholesterol (mg/dL)	-0.020	NS
LDL-cholesterol (mg/dL)	-0.020	NS
HDL-cholesterol (mg/dL)	-0.011	NS
Triglycerides (mg/dL)	-0.033	NS
Creatinine (mg/dL)	0.041	NS
Glucose (mg/dL)	-0.203	0.020
Urinary albumin excretion (µg/min)	-0.154	NS
Creatinine clearance (ml/min)	-0.022	NS
Left ventricular mass (g)	-0.008	NS
Left ventricular mass index (g/m²)	0.130	NS

SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – Heart rate; rSBP2 – Late systolic BP in the radial artery (central pressure); PP – Pulse pressure; NS – Not significant (p > 0.05).

Table 5 – Multivariate relation between augmentation index and clinical-biochemical variables

Variable	ß	SEß	p value
Weight (Kg)	-0.001	0.001	0.017
Height (m)	-0.019	0.089	NS
Gender	0.010	0.015	NS
SBP (mm Hg)	-0.011	0.020	NS
DBP (mm Hg)	-0.002	0.020	NS
HR (beats/min)	-0.001	0.001	0.007
PP (mm Hg)	-0.001	0.020	NS
rSBP2 (mmHg)	0.015	0.001	< 0.001
Glucose (mg/dL)	0.001	0.001	NS

SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – Heart rate; PP – Pulse pressure; rSBP2 – Late systolic BP in the radial artery (central pressure); NS – Not significant (p > 0.05).

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