

Aortic Stiffness is an Independent Predictor of Stroke in Hypertensive Patients

Telmo Pereira^{1,2}, João Maldonado³, Liliana Pereira¹, Jorge Conde¹

Escola Superior de Tecnologia da Saúde de Coimbra - Departamento de Cardiopneumologia¹, Coimbra, Portugal; Universidade Metodista de Angola - Departamento de Cardiopneumologia - Faculdade de Ciências da Saúde², Luanda, Angola; Instituto de Investigação e Formação Cardiovascular³, Coimbra – Portugal

Abstract

Background: Cardiovascular disease remains the leading cause of death in developed countries and is not entirely predicted by classic risk factors. Increased arterial stiffness is an important determinant of cardiovascular morbidity and mortality.

Objective: To assess whether Aortic Pulse Wave Velocity (PWV) predicts the occurrence of stroke in hypertensive patients.

Methods: A cohort, observational and prospective study, including 1133 hypertensive patients (586 men), with a mean age 51.05 ± 12.64 years, was designed. PWV with the Complior method was performed in all patients, as well as a detailed clinical evaluation and blood pressure measurement.

Results: The cumulative incidence of stroke in hypertensive patients with increased PWV was 3.25% (CI: 1.97% -5.25%), compared with 0.78% (CI: 0.28% -1.87%) in hypertensive patients with normal PWV (Risk Ratio (RR) = 4.15; CI:1.53-11.26). In a multivariate analysis, adjusting the model to classical cardiovascular risk factors, PWV was an independent predictor of stroke, with a Hazard Ratio (HR) = 1.40 (CI:1.13-1.73, $p < 0.001$), indicating a 40% increase in the risk of stroke per 1m/s increment in PWV. The addition of PWV to a model consisting of conventional cardiovascular risk factors significantly improved the discriminative capacity for stroke (Harrell's C increased from 0.68 to 0.71 after the inclusion of the PWV; $p < 0.01$).

Conclusion: Aortic PWV is a risk factor for stroke in hypertensive patients, and its integration into clinical follow-up programs in patients whose cardiovascular risk is manifest is strongly recommended (Arq Bras Cardiol. 2013; 100(5):437-443).

Keywords: Vascular Stiffness; Hypertension; Aorta / abnormalities; Stroke.

Introduction

Systemic arterial hypertension (SAH) is one of the main risk factors for cardiovascular diseases, and is closely related to stroke and coronary disease¹⁻³. The advancing knowledge in SAH allow us to consider it a systemic disease associated to endothelial function, arterial elasticity, arterial wall structure and myocardial changes^{4,5}. Thus, SAH is the most important stroke risk factor, due to at least three reasons: focal damage to intracerebral arteries (lipohyalinosis), leading ultimately to arterial occlusion; ischemic necrosis and the subsequent appearance of small brain cavities (lacunar infarcts); and small intracerebral arteries rupture, leading to cerebral hemorrhages^{6,7}. SAH also promotes media hypertrophy and thickening in the small intracerebral arteries and diffuse ischemic rarefaction and hypoperfusion of the white matter⁷.

The increased arterial stiffness is one of the pathophysiological vectors of SAH, contributing to the enhanced cardiovascular risk by increasing systolic blood pressure (SBP) and reducing diastolic blood pressure (DBP), leading to arterial hyperpulsatility, whose most important hemodynamic paradigm is the increased pulse pressure (PP)⁸. Thus, the previously described association between cardiovascular risk and PP is related to a pathophysiological context that includes the great central arteries reduced distensibility, of which this hemodynamic variable is a rough and poorly sensitive indicator. Therefore, arterial stiffness can be non-invasively evaluated by the aortic pulse wave velocity (PWV), a rigorous technique with solid experimental support⁹. From a clinical point of view, studies have shown that PWV is an independent cardiovascular risk marker in various clinical contexts^{1,8-11}. This association is largely derived from the adverse effects exerted by the arterial stiffness over central circulation and the interaction between the left ventricle (LV) and the aorta^{12,13}. The aim of this study is to verify if PWV predicts stroke in hypertensive patients, on top of the traditional cardiovascular risk factors.

Mailing Address: Telmo Pereira •

Rua General Humberto Delgado, 102, Lousa. Postal Code 3200-107, Coimbra - Portugal

E-mail: telmopereira@spc.pt, telmo@estescoimbra.pt

Manuscript received August 02, 2012; revised manuscript September 01, 2012; accepted November 11, 2012.

DOI: 10.5935/abc.20130079

Methods

Study population

A sample of 1133 Portuguese hypertensive patients (586 men and 547 women), with mean age of 51.05 ± 12.64 years (ranging from 19 to 84 years old), was included in an observational, prospective and multicentric cohort study. All the participants were chronically taking drugs for treating SAH. The study's objectives were explained to all the participants, and the respective informed consent was obtained.

All participants were followed for 24 months for verifying the occurrence of major cardiovascular events, such as stroke, acute myocardial infarction (AMI), peripheral artery disease, revascularization and cardiac or renal failure. All individuals were submitted to biometric evaluation (height, weight, and body mass index). Blood pressure was controlled in all participants. All patients were also submitted to routine blood tests and aortic PWV determination. Information was collected on smoking habits, alcohol consumption and drugs taken.

The study was approved by the Ethics Committees of the Institutions involved, in compliance with the Declaration of Helsinki.

Blood pressure measurement

Blood pressure was measured at rest at the humeral artery, after resting for 10 minutes in supine position. A clinically validated automatic device (Class A - Colson MAM BP 3AA1-2®; Colson, Paris)¹⁴, with a cuff adjusted to arm circumference, was used for measuring blood pressure. Three consecutive measurements were done on the right arm, with an interval of one minute between them, and the mean was calculated. Systolic, diastolic, mean and differential blood pressures were considered in the analysis, as well as heart rate. The differential pressure was calculated as the difference between SBP and DBP, and mean arterial blood pressure (MBP) was obtained by the equation $MBP = DBP + 1/3 PP$.

Pulse wave velocity

Aortic distensibility was evaluated by means of the aortic pulse wave velocity (PWV) determination with the Complior® device (Colson, Paris), according to a previously described technique¹⁵. Briefly, PWV was calculated by the distance/time rate (m/s), simultaneously measuring the right carotid artery and the right femoral artery pulse wave velocities. PWVs were determined by the same operator and the quality of the measurements was verified by two independent observers with large experience in this measurement. The previously determined reproducibility of these estimates in our laboratory comprises correlation coefficients higher than 0.9 (0.98 and 0.95, respectively, for inter- and intra-observer differences)¹⁶. Normal PWV definition was based on the recently published normal values for the Portuguese population, a statistic definition based on the 95th percentile adjusted to age and gender and determined on a sample of healthy individuals¹⁷.

Statistical analysis

Patients' data was computerized and treated with STATA software for Windows, version 11.0. The variables were tested for normal distribution by the Kolmogorov-Smirnov test and, for variance homogeneity, by the Levene test. Simple descriptive statistics were used for the general characterization of the sample and variable distribution. ROC (receiver operating characteristic) curves were used for evaluating the global prognostic/discriminatory capacity of PWC in stroke. Survival curves were estimated by the Kaplan-Meier method, and the groups were compared using the log-rank test. Cox regression analysis was applied to determine the influence of PWV in the defined event occurrence, after verifying compliance to the risk proportionality statistic requirements. Measurements for model adjustment (likelihood ratio test, Akaike information criterion and Schwartz Bayesian information criterion), discrimination (Harrel's C coefficient) and calibration (Hosmer-Lemeshow test) were estimated to allow the comparison of the discriminative power of PWV.

Comparisons between groups were done by the χ^2 test for categorical variables, or the Student's t test (2 groups) or ANOVA Tukey's post-hoc test (3 groups) with quantitative variable with normal distribution.

The statistical significance criterion was a value of $p \leq 0.5$ with a 95% confidence interval.

Results

The general characteristics of the hypertensive study population are summarized in Table 1.

Mean age was 51.05 ± 12.64 years old, ranging from 19 to 91, with similar proportions observed among men and women (51.7% and 48.3%, respectively).

Regarding cardiovascular risk factors, 30% of the patients had dyslipidemia, 12% were diabetic, 10% were smokers and 2% had a stroke during the follow-up period.

PWV was considered normal or abnormal according to previously published normal criteria for the Portuguese population¹⁷. The high PWV group had higher mean age, higher BMI, higher blood pressure levels and a higher proportion of diabetic patients. Curiously, the smoker's rate was lower.

Figure 1 shows the Kaplan-Meier survival curve for stroke-free survival, according to PWV category. A clear difference can be observed between groups so that, after two years' follow-up, stroke-free survival is greater in patients with normal PWV (approximately 99.22%), as compared to the 96.75% found in the increased PWV group. Thus, the cumulative stroke incidence in the increased PWV group was 3.25% (CI: 1.97%-5.25%), compared to 0.78% (CI: 0.28% - 1.87%) in the normal PWV group, a relative risk (RR) of 4.15 (CI: 1.53 - 11.26), a risk difference of 2.46% (CI: 0.76% - 4.17%) and a risk etiologic fraction of 75.93% (CI: 34.75% - 91.12%) in patients with increased PWV.

Table 1 - General cohort characteristics according to pulse wave velocity classification

	Total (n = 1133)	Normal PWV (n = 640)	Increased PWV (n = 493)	p (between groups)
Age (years)	51.05 - 12.64	48.88 - 12.99	53.86 - 11.58	< 0.001
Gender (F/M)*	48/52	45/55	53/47	< 0.001
BMI (kg/m ²)	28.02 ± 4.61	27.41 ± 4.08	28.82 ± 5.11	< 0.001
PWV (m/s)	10.72 ± 2.04	9.36 ± 1.16	12.48 ± 1.54	< 0.001
SBP (mmHg)	150.88 ± 20.87	145.91 ± 19.44	157.34 ± 20.92	< 0.001
DBP (mmHg)	88.62 ± 11.6	86.9 ± 11.28	90.83 ± 11.6	< 0.001
MBP (mmHg)	109.47 ± 13.28	106.58 ± 12.7	113.2 ± 13.09	< 0.001
PP (mmHg)	62.12 ± 16.49	58.99 ± 14.9	113.2 ± 13.09	< 0.001
HR (bpm)	72.26 ± 11.45	71.50 ± 11.1	73.2 ± 11.8	< 0.011
Weight (kg)	76.42 ± 14.01	75.67 ± 13.81	77.39 ± 14.22	< 0.040
Height (m)	1.65 ± 0.09	1.66 ± 0.09	1.64 ± 0.08	< 0.001
Smoker (N/Y)*	90/10	89/11	92/8	< 0.110
Diabetes (N/Y)*	88/12	90/10	86/14	< 0.078
Dyslipidemia (N/Y)*	70/30	71/29	70/30	< 0.743
Stroke (N/Y)*	98/2	99/1	97/3	< 0.003

BMI: body mass index; DBP: diastolic blood pressure; F/M: female/male; HR: heart rate; MBP: mean blood pressure; N/Y: no/yes; PP: pulse pressure; PWV: pulse wave velocity; SBP: systolic blood pressure; *, %.

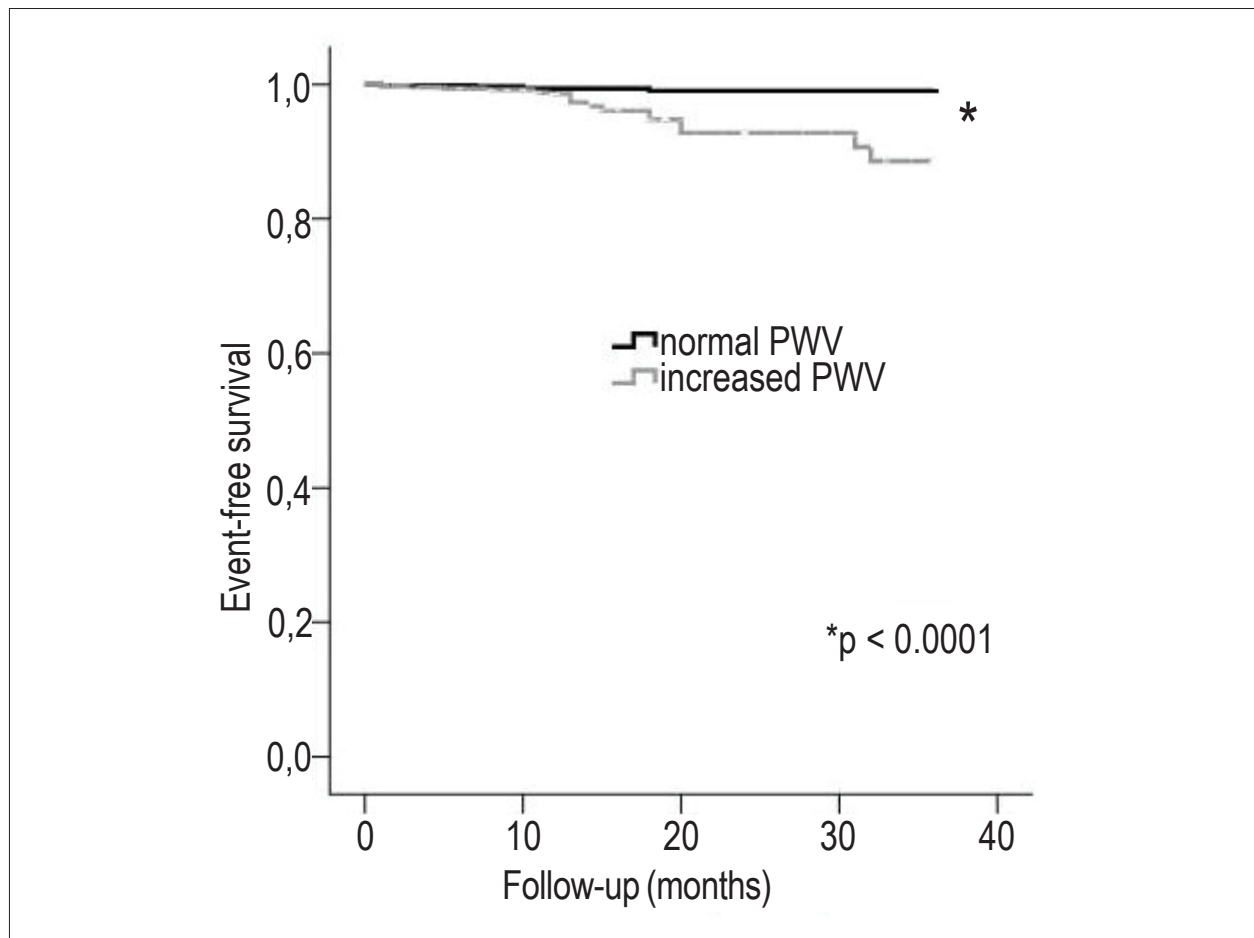


Figure 1 - Stroke-free survival curve according to pulse wave velocity classification. PWV: pulse wave velocity.

Cox regression analysis was used to identify the main determinants of stroke occurrence in the analyzed cohort. At the univariate analysis for stroke occurrence (see Table 2) based on the risk factors age, gender, BMI, MBP, diabetes, dyslipidemia, smoking status and PWV (classified according to the 95th percentile), a statistically significant association was found between PWV and stroke, with a hazard ratio (HR) of 5.29 (CI: 1.93-14.54). A HR of 1.29 (CI: 1.07-1.55) was obtained taking into account the absolute relationship of stroke risk and PWV.

PWV remained as an independent stroke predictor with an HR of 4.89 (CI: 1.71 - 14) in the multivariate regression analysis (Table 3), adjusting the model for conventional cardiovascular risk factors. When the multivariate analysis was replicated adding PWV as a continuous variable, an increase of 40% of the stroke risk was verified for each 1 m/s increase in PWV, independently from other cardiovascular risk factor (HR = 1.40; 1.13 - 1.73; $p = 0.002$).

We performed a complementary analysis for model adjustment (summarized on Table 4) in order to evaluate how the addition of PWV to the classic risk factors would improve the discriminative capacity for stroke.

When aortic PWV was added to age and gender, a significant improvement was observed in stroke occurrence discrimination, as described in the measurements considered while adjusting the model. The C coefficient improved from 0.61 to 0.69 after PWV was added to the model, a change translated as an improvement in risk discrimination. We have also verified that adding PWV led to a global improvement in the discrimination capacity of the presented model, an aspect that was reinforced by the reduction observed in the Akaike information criteria and Schwartz Bayesian information criterion. Adding PWV to a risk model that included age, gender, BMI, smoking status, diabetes mellitus, dyslipidemia, and MBP led equally to a significant improvement in the global discrimination capacity, an increase of the C coefficient (from 0.68 to 0.71) and an improvement of the other calibration and model adjustment indicators (see Table 4). Globally, we can observe that the discriminative capacity improved in the tested models, indicating clearly that PWV is to be considered a risk factor in stroke risk stratification in hypertensive patients.

Discussion

Arterial distensibility is an important field in cardiovascular research, particularly due to its value in risk stratification in various clinical situations. PWV is definitely the best indicator of aortic stiffness and is unequivocally related to cardiovascular mortality and morbidity in patients with diabetes, hypertension, the elderly and the general population¹⁸⁻²¹.

One of the first studies to provide direct evidence of the association of aortic stiffness with global and cardiovascular mortality in hypertensive patients was published in 2001¹⁹. In this study, PWV was significantly associated with global and cardiovascular mortality in an univariate logistic regression model; this association was demonstrated by an odds ratio (OR) of, respectively, 2.14 (CI: 1.71-2.67, $p < 0.0001$) and 2.35 (CI: 1.76-3.14, $p < 0.0001$) for each

1 SD of aortic PWV. In the multivariate logistic regression models, PWV was significantly associated with death due to all causes, independent from other risk factors, such as age and diabetes.

More recently, the EDIVA study confirmed PWV as an independent marker of cardiovascular risk in the general population, with an adjusted HR of 1.316 for each 1 m/s increase in PWV⁵.

The present study's results add to the available evidence and make PWV unequivocally important for cardiovascular risk stratification in the hypertensive population, on top of the conventional cardiovascular risk factors. Indeed, when PWV was added to the discrimination and adjustment model, clear improvement was verified in the model's calibration and scoring criteria. Globally, discriminative capacity improved as PWV was incorporated in the model, clearly indicating that, more than a marker of organ subclinical damage^{19,21,22}, aortic PWV is, above all, a true stroke risk factor. The high discriminative power of PWV was corroborated by Kaplan-Meier analysis that showed better stroke-free survival in hypertensive patients with normal PWV. For that matter, multivariate Cox regression analysis places PWV as an independent determining factor for stroke, increasing the risk of this cardiovascular event approximately 40% for each 1 m/s increase in PWV.

A number of studies with similar objectives have been published in the last few years, showing a strong association between PWV increase and stroke and cardiovascular complications in patients with high blood pressure^{5,14,18}.

Various mechanisms can explain the association between PWC increase and stroke. First, arterial stiffness can favor the occurrence of cerebrovascular events by increasing PP at the central region. PP amplitude can influence intra- and extracranial arteries remodeling, increasing carotid wall thickness, promoting atherosclerosis, increasing the likelihood of vulnerable plaque rupture and contributing significantly to the prevalence and severity of white matter brain lesions. Both atherosclerosis and the plaques that appear as a consequence to the common thickness increase of the intima and media layers in the carotid walls are indeed related to white matter brain lesions.

Second, aortic stiffness measurements, including arterial wall changes, may also reflect systemic arterial lesions. In fact, the aortic stiffness related to age and other cardiovascular risk factors has numerous causes, such as fibrosis, medial smooth muscle necrosis, elastin fiber rupture, calcifications and macromolecule diffusion within the arterial wall, factors that have already been described in the brain vasculature. Third, heart failure and coronary disease, favored by high PP and arterial stiffness, are also risk factors for stroke¹⁸.

Taking into account current evidence, the relationship between PWV and cardiovascular risk factors is clear, and PWC can be considered a powerful stroke risk indicator and an excellent independent stroke predictor. The reported results allow the consolidation of the role of this hemodynamic parameter in stroke risk stratification, clearly indicating that PWV is, more than an organ lesion marker, a true independent risk factor. Thus, the incorporation of the arterial distensibility concept in clinical practice and its diffusion aiming to optimize clinical decision is imperative, especially at the primary prevention level.

Table 2 - Univariate analysis for stroke occurrence

Parameters	Hazard Ratio	CI	p
Gender (male - reference)	0.48	0.19-1.16	0.102
Age (years)	0.99	0.95-1.02	0.470
MBP (mmHg)	1.046	1.01-1.080	0.008
BMI (kg/m ²)	0.944	0.846-1.053	0.301
Dyslipidemia (No - reference)	0.804	0.32-2.04	0.645
Diabetes (No - reference)	3.720	0.496-27.877	0.201
Smoker (No - reference)	0.85	0.196-3.654	0.822
Categorized PWV (normal - reference)	5.29	1.93-14.54	0.001
PWV (m/s)	1.29	1.07-1.55	0.008

BMI: body mass index; CI: confidence interval; MBP: mean blood pressure; PWV: pulse wave velocity.

Table 3 - Multivariate analysis for stroke occurrence

Parameters	Hazard Ratio	CI	p
Categorized PWV	4.89	1.71 - 14	0.003
Gender	1.812	0.72 - 4.58	0.205
Age	0.977	0.941 - 1.015	0.233
MBP (mmHg)	1.037	1.002 - 1.073	0.039
Diabetes	3.639	0.468 - 28.32	0.217
Dyslipidemia	1.17	0.44 - 3.14	0.753
BMI (kg/m ²)	0.95	0.86 - 1.05	0.299
Smoker	1.052	0.23 - 4.83	0.095
PWV (m/s)	1.40	1.13 - 1.73	0.002

BMI: body mass index; CI: confidence interval; MBP: mean blood pressure; PWV: pulse wave velocity.

Table 4 - Adjustment coefficients of the model, discrimination and calibration for stroke occurrence after incorporation of aortic PWV

Model	Model adjustment			Discrimination	Calibration	
	-2 Log Likelihood	Akaike Information Criterion	Schwartz's Bayesian Information Criterion	C Statistic	X ²	p
Gender, age	133.449	270.8971	280.9624	0.61	8.51	0.39
Adding PWV	- 128.01	262.0289	277.1268	0.69	5.15	0.74
Age, gender, BMI, smokers Diabetes mellitus, dyslipidemia, MBP	- 128.19616	270.39	305.62	0.68	7.97	0.44
Adding PWV	-123.997	263.895	304.156	0.71	2.86	0.95

BMI: body mass index; MBP: mean blood pressure; PWV: pulse wave velocity.

It is not clear whether PWV should constitute a therapeutic target, and the most adequate drugs for positive modulation of the arterial physiology in this particular pathophysiological context remain to be identified. Future studies having PWV as an endpoint

will allow us to answer this fundamental issue. On the other side, better standardization of arterial stiffness evaluation methods is needed, as well as adherence to the main recommendations guiding the application of these concepts¹⁵.

Conclusion

Aortic PWV analysis has established itself as a true cardiovascular risk factor, emerging as an attractive and simple manner of broadening the arterial stiffness concept and adapting it to daily clinical practice, contributing decisively to improve cardiovascular and, particularly, stroke risk evaluation.

Author contributions

Conception and design of the research and Acquisition of data: Pereira T, Maldonado J; Analysis and interpretation of the data: Pereira T, Maldonado J, Pereira L; Statistical analysis and Writing of the manuscript: Pereira T, Pereira L; Critical revision of the manuscript for intellectual content: Maldonado J, Conde J.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

References

1. Pizzi O, Brandão AA, Magalhães ME, Pozzan R, Brandão AP. Pulse wave velocity - methodology and prognostic implications in hypertension. *Rev Bras Hipertens.* 2006;13(1):59-62.
2. Blacher J, Guérin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation.* 1999;99(18):2434-9.
3. Mattace-Raso F, Hofman A, Verwoert GC, Wittemana JC, Wilkinson I, Cockcroft J, et al; Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: establishing normal and reference values. *Eur Heart J.* 2010;31(19):2338-50.
4. Bortolotto L. Role of arterial stiffness in cardiovascular risk of hypertensive patient. *Rev Bras Hipertens.* 2007;14(1):46-7.
5. Maldonado J, Pereira T, Polónia J, Silva J, Morais J, Marques M; participants in the EDIVA Project. Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de Distensibilidade Vascular) project. *J Hypertens.* 2011;29(4):669-75.
6. Bortolotto LA, Safar ME. [Blood pressure profile along the arterial tree and genetics of hypertension]. *Arq Bras Cardiol.* 2006;86(3):166-9.
7. Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, et al. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. *Circ J.* 2005;69(3):259-64.
8. Bortolotto LA, Blacher J, Kondo T, Takazawa K, Safar ME. Assessment of vascular aging and atherosclerosis in hypertensive subjects: second derivative of photoplethysmogram versus pulse wave velocity. *Am J Hypertens.* 2000;13(2):165-71.
9. Bastos JM, Bertoquini S, Polonia 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(9):1287-303.
10. Pizzi OL, Brandão AA, Pozzan R, Magalhães ME, Freitas EV, Brandão AP. Pulse wave velocity in young adults: study of Rio de Janeiro. *Arq Bras Cardiol.* 2011;97(1):53-8.
11. Rocha E. [Pulse wave velocity: a marker of arterial stiffness and its applicability in clinical practice]. *Rev Port Cardiol.* 2011;30(9):699-702.
12. Gómez-Marcos MA, Recio-Rodríguez JJ, Rodríguez-Sánchez E, Castaño-Sánchez Y, de Cabo-Laso A, Sánchez-Salgado B, et al. Central blood pressure and pulse wave velocity: relationship to target organ damage and cardiovascular morbidity- mortality in diabetic patients or metabolic syndrome. LOD-DIABETES study protocol. An observational prospective study. *BMC Public Health.* 2010;10:143.
13. Pabuccu T, Baris N, Ozpelit E, Akdeniz B, Guneri S. The relationship between resistant hypertension and arterial stiffness. *Clin Exp Hypertens.* 2012;34(1):57-62.
14. Pereira T, Maldonado J. Performance of the Colson MAM BP 3AA1-2 automatic blood pressure monitor according to the European Society of Hypertension validation protocol. *Rev Port Cardiol.* 2005;24(11):1341-51.
15. Maldonado J, Pego M, Bastos M, Guimarães H, Monteiro V, Providência LA. [Pulse wave velocity as expression of arterial compliance and its importance in the evaluation of arterial hypertension]. *Rev Port Cardiol.* 1992;11(11):929-32.
16. Pereira T, Maldonado J. Comparative study of two generations of the Complior device for aortic pulse wave velocity measurements. *Blood Press Monit.* 2010;15(6):316-21.
17. Pereira T, Maldonado J, Polónia J, Alberto Silva J, Morais J, Marques M; Projecto EDIVA. Definição de valores de referência da velocidade da onda de pulso arterial numa população portuguesa: uma sub-análise do projecto EDIVA. *Rev Port Cardiol.* 2011;30(9):691-8.
18. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke.* 2003;34(5):1203-6.
19. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension.* 2002;37(5):1236-41.
20. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects > 70 years of age. *Arterioscler Thromb Vasc Biol.* 2001;21(12):2046-50.
21. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension.* 2002;39(1):10-5.
22. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al; The task force for the management of arterial hypertension of the European Society of Hypertension, The task force for the management of arterial hypertension of the European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2007;28(12):1462-536.