PERIPHERAL ARTERIAL STIFFNESS IN PRIMARY ALDOSTERONISM

Jan Rosa[1,2], Zuzana Somloova[1], Ondrej Petrak[1], Branislav Strauch[1], Tomas Indra[1], Michal Senitko[3], Tomas Zelinka[1], Robert Holaj[1], Jiri Widimsky jr.[1]

[1]3rd Department of Internal Medicine, General Faculty Hospital, First Medical Faculty, Charles University, Prague;

[2]3rd Department of Internal Medicine, University Hospital Kralovske Vinohrady, Third Medical Faculty, Charles University, Prague and

[3]Department of Medicine, University of Mississippi Medical Center, Jackson, USA.

Correspondence to: Jan Rosa, 3rd Department of Internal Medicine, General Faculty Hospital, U Nemocnice 2, 128 08 Prague, Czech Republic, tel.:+420224962945, fax:+420224963245, email: jan.rosa@lf1.cuni.cz

Short title: Peripheral pulse wave velocity in primary aldosteronism

SUMMARY

Aldosterone overproduction increases arterial wall stiffness by accumulation of different types of collagen fibres and growth factors. Our previous studies showed that central (aortic) arterial stiffness is increased in primary aldosteronism (PA) independently of concomitant hypertension and that these changes might be reversible after successful adrenalectomy. There is limited data available on the potential impact of mineralocorticoid overproduction on the deterioration of peripheral arterial stiffness. The current study was thus aimed at investigating the effect of aldosterone overproduction on peripheral arterial stiffness assessed by peripheral (femoral-ankle) pulse wave velocity (PWV) in PA patients compared with essential hypertension (EH) patients.

Forty-nine patients with confirmed PA and 49 patients with EH were matched for age, blood pressure, body mass index, lipid profile, and fasting glucose. PWV was obtained using the Sphygmocor applanation tonometer.

Both peripheral and central PWV were significantly higher in PA patients compared to EH patients, while clinical blood pressures were similar. Plasma aldosterone level was the main predictor of peripheral PWV in PA.

Our data indicate aldosterone overproduction in PA does not preferentially affect central arterial system. Fibroproliferative effect of higher aldosterone levels lead to alteration of central-elastic as well as peripheral-muscular arteries with subsequent increase in its stiffness.

KEYWORDS: peripheral arterial stiffness, primary aldosteronism, peripheral pulse wave velocity

INTRODUCTION

Primary aldosteronism (PA) is characterized by the autonomous overproduction of aldosterone by the adrenal glands generally caused by adrenocortical adenoma or bilateral adrenal hyperplasia. The prevalence of PA in patients with any stage of hypertension varies from 5 to 15% (Funder *et al.* 2008; Mulatero *et al.* 2011; Rossi 2010; Takeda *et al.* 2011). We have previously shown that PA is the most frequent form of secondary hypertension with a prevalence of 19% in moderate to severe hypertension (Strauch *et al.* 2003) among patients admitted to our hypertension unit.

Previous studies also indicated that patients with PA might be at higher cardiovascular risk than patients with essential hypertension (EH) (Catena *et al.* 2008). Increased left ventricular mass, significant impairment of diastolic dysfunction (Rossi *et al.* 1996), more frequent renal function impairment (Wu *et al.* 2011), increased intima-media thickness of common carotid arteries (Holaj *et al.* 2007), or impaired diurnal blood pressure variation (Zelinka *et al.* 2004) are all present more frequently in patients with PA than in EH.

Aldosterone overproduction leads to functional and structural changes of arterial system. Animal models demonstrate that aldosterone substantially contributes to the accumulation of different types of collagen fibres and growth factors in vascular smooth muscle cells. Aldosterone receptor antagonists (e.g. spironolactone) may prevent or be able to reverse these changes (Martin-Fernandez *et al.* 2011). However, there are limited studies examining aldosterone effect on vascular changes in humans (Joffe and Adler 2005; Mahmud and Feely 2005). Different effect of aldosterone overproduction might be present in different segments of arterial tree with changing vascular wall’s composition.

The prognostic value of central arterial stiffness is well established (Mitchell *et al.* 2010) and aortic pulse wave velocity (PWV) predicts cardiovascular mortality and morbidity beyond classical risk factors (Vlachopoulos *et al.* 2010). However, there are currently limited studies dealing with the predictive value of peripheral arterial stiffness for cardiovascular morbidity and this relationship remains unclear (Bernini *et al.* 2008; Choi *et al.* 2010; Khandanpour *et al.* 2009; Tsuchikura *et al.* 2010). Peripheral arterial stiffness investigation might be valuable in screening for and evaluating the severity of peripheral arterial disease (Khandanpour *et al.* 2009). On the other hand, the preferential increase in central arterial stiffness is found not only in coronary artery disease but in cerebrovascular disease and peripheral artery disease as well (Tsuchikura *et al.* 2010). Similarly, aging has a greater effect on the central than the peripheral arterial system (Choi *et al.* 2010).

Patients with PA had greater aortic wall stiffness by PWV compared to EH patients in our previous study (Strauch *et al.* 2006). Similar results were seen in the study by Bernini et al. (Bernini *et al.* 2008) and specific treatment with adrenalectomy might reverse these changes (Strauch *et al.* 2008). There is lack of data concerning the relationship between aldosterone overproduction and changes in peripheral, muscular arteries in humans. The current study was thus aimed at investigating the effect of aldosterone overproduction on peripheral arterial stiffness assessed by femoral-ankle PWV in PA patients in comparison to EH patients.

METHODS

Study population

A total of 49 patients with confirmed PA and 49 patients with EH were assessed. The examination of all subjects was performed after discontinuation of their usual antihypertensive therapy. Patients were switched to an alpha-blocker (doxazosine) and/or slow-release calcium channel blocker (verapamil) at least 14 days prior to admission to eliminate the interference of other antihypertensive drugs with the renin–angiotensin–aldosterone system (RAAS). Spironolactone was stopped 6 weeks before investigation. This wash out period is generally accepted in PA diagnosis algorithm (Funder *et al.* 2008).The screening for the diagnosis of PA was based on an elevated aldosterone-to-renin ratio (ARR) ≥40 ((ng/dl)/(ng/ml/h)) when plasma renin activity (PRA) and aldosterone levels were measured post 2hours in the upright position also with suppressed PRA (≤0.7 ng/ml/h) and elevated plasma aldosterone (≥15 ng/dl). The diagnosis of PA was confirmed by the absence of plasma aldosterone suppression (plasma aldosterone $\leq$ 7 ng/dl) after saline infusion (2 liters 0.9% saline infused over 4 hours) (Funder *et al.* 2008; Mulatero *et al.* 2011).

The diagnosis of EH was made by exclusion of the most common forms of secondary hypertension (PA, pheochromocytoma, Cushing's syndrome, renal parenchymal disease and renovascular hypertension). PA was excluded according to normal ARR and aldosterone suppression presence after saline infusion.

Pulse wave velocity

All subjects underwent PWV assessment with the applanation tonometer

Sphygmocor (AtCor Medical, Australia). Subjects were studied by a single examiner after overnight fasting and after a 15minute resting period, during which the patient was in a supine position in a quiet room. Central (aortic) PWV was assessed by the time difference between pulse wave upstrokes consecutively measured at the right common carotid artery and right femoral artery, then aligned by the ECG-based trigger. The 'percentage pulse height algorithm' was used to locate the foot of the pulse waves. To determine the distance between measured sites subtraction method was used (sternal notch to femoral site minus sternal notch to carotid site). Similarly, peripheral femoral-ankle PWV (pPWV) was assessed by the time difference between pulse wave upstrokes measured at the right femoral artery and right tibial anterior or posterior artery.

Blood pressure measurements

Clinical blood pressure values were obtained using an oscillometric sphygmomanometer (Dinamap, Critikon, Tampa, FL, USA) according to European Society of Hypertension Guidelines just before PWV measurement (Mancia *et al.* 2007). Twenty-four hour ambulatory blood pressure monitoring (ABPM) during hospitalization was performed using an oscillometric device (SpaceLabs 90207; SpaceLabs Medical, Redmond, WA, USA). This was not performed during the saline infusion load.**Laboratory tests**

All hormonal tests were performed by radioimmunoanalysis using commercially available kits (Immunotech, Beckman Coulter Company, Prague, Czech Republic). All other biochemical parameters were analyzed using multianalyzers (Hitachi 717, Boehringer Mannheim, Germany) in the Institutional Central Laboratory.

Statistical analysis

Depending on the normal/non-normal distribution (Shapiro–Wilks W-test) of individual variables, the results are shown as means ± standard deviations or medians (interquartile range). Between-group comparisons were performed by two-tailed t-test for independent samples. The Kruskal–Wallis test was used for non-normally distributed variables. Pearson's correlation analysis and multiple regression analysis (stepwise forward method) were applied to assess the relationship among central PWV/pPWV and clinical/laboratory parameters (variables which significantly correlated in Pearson's correlation analysis entered multiple regression analysis). For between-group central PWV/pPWV comparisons, a multivariate regression model was used to adjust for confounding indices. P-value <0.05 was considered to be significant. The statistical analysis was performed by STATISTICA software version 8 (StatSoft, Tulsa, OK, USA).

RESULTS

The basic clinical characteristics of studied groups are shown in Table 1. There were no significant differences in age, duration of hypertension, body mass index, lipid profile, fasting glucose levels, or creatinine levels between PA and EH groups. As expected, plasma potassium and PRA levels were significantly lower in PA participants and similarly, plasma aldosterone, ARR, and sodium levels were higher. Microalbuminuria was significantly higher in PA patients, however, there were no differences in creatinine clearance corrected for body surface area or estimated glomerular filtration (according to Cockroft-Gault formula). Both groups were comparable in dyslipidemia, diabetes mellitus type 2 occurrence, as well as in statins

and antidiabetic agents use. The differences in hemodynamic parameters and pulse wave indices are summarized in Table 2. Both peripheral (11.59 vs. 10.7 m/s, p<0,005) and central PWV (8.7 vs. 8.0 m/s, p=0.023) were significantly higher in PA when compared to EH patients, while clinical blood pressure was comparable (154/89 vs. 150/89 mmHg, p>0.05). The results are illustrated in Figure 1 and Table 2. Despite the fact, that PA patients had significantly higher 24 hour ambulatory BP than EH, this difference remained significant after adjustments for age, clinical and 24h mean blood pressure (p=0.018 for pPWV; p=0.026 for central PWV). After multiple regression analysis, aldosterone levels appeared to be the main predictor of pPWV, while age and clinical systolic BP were the main predictors of central PWV in PA. On the other hand, increased PRA with 24-hour diastolic BP and age with pulse pressure were the main predictors of pPWV and central PWV, respectively, in EH patients. Unlike EH patients, no relationship among 24hour blood pressure indices and central/peripheral PWV was found in PA patients after multiple regression analysis. Table 3 summarizes the results of multiple regression analysis. Using logistic regression analysis for PA, central and peripheral PWV seem to be most important determinants of PA. See Table 4 for results.

DISCUSSION

The effect of aldosterone overproduction may contribute to increased aortic stiffness and to higher intima-media thickness of carotid arteries (Holaj *et al.* 2007; Strauch *et al.* 2006). Furthermore, increased aortic stiffness might be reversible after successful treatment with adrenalectomy (Strauch *et al.* 2008).

The results of this investigation demonstrated higher central and peripheral arterial stiffness in PA patients in comparison to EH patients. Fibroproliferative effects

of higher aldosterone levels might lead to alteration of central-elastic as well as peripheral-muscular arteries with subsequent increase in arterial stiffness. Total collagen and type III vascular collagen were found significantly higher in PA patients than in EH in small resistance arteries (Rizzoni *et al.* 2006). Similar changes might be expected in greater muscular and elastic arteries.

In vitro or animal studies proved fibroproliferative effects of aldosterone with accumulation of different types of collagen fibers and growth factors in vascular smooth muscle cell. However, there is lack of evidence of a direct relation between vascular stiffness and plasma aldosterone levels in humans and also no correlation between plasma aldosterone level and the morpho-functional parameters was found (Bernini *et al.* 2008; Joffe *et al.* 2005; Mahmud *et al.* 2005). Positive correlations were found between the ARR and parameters of pulse wave analysis (which represents systemic arterial stiffness) and its parameters, e.g. central blood pressure and augmentation index. These parameters are all related to cardiovascular diseases (CVD) to a similar extent as classic CVD risk factors. However PWV is considered to be a more precise marker of arterial stiffness(Mitchell *et al.* 2010), but there are no correlations between ARR and PWV (Mahmud *et al.* 2005). This might be explained by the hypothesis that aldosterone levels detected during the examination may not correspond to the chronic impact of aldosteronism prior to diagnosis of PA. Also, circulating aldosterone levels do not reflect local aldosterone effect on the vascular wall and plasma aldosterone levels may not reflect the local production of aldosterone in the vascular wall. In our study, multiple regression analysis showed, that plasma aldosterone level might be one of the most important predictors of peripheral PWV in PA. This fact and the finding of correlation of PRA after multiple regression analysis in EH suggest the importance of the role of RAAS in peripheral arterial stiffness.

However, no similar correlations were found in central PWV, neither in PA, nor in EH. Age and clinical blood pressure parameters seem to be the most important predictors of aortic PWV. These results suggest possible different effect and different mechanisms of action of aldosterone overproduction on central and peripheral arteries. There are several explanations, but the exact mechanisms are not clear. Some vascular changes might be the result of aldosterone induced higher blood pressure load, but it seems that changes are independent of actions that can be attributed to blood pressure rise (Schiffrin 2006; Williams 2005). The results might be explained by different effects of aldosterone on different parts of arterial tree with different composition of vessel wall. Either delayed (genomic) or rapid (nongenomic) mechanisms of action of aldosterone might be involved as well.

As expected, higher serum sodium and lower serum potassium levels were found in PA group as a result of aldosterone overproduction. Similarly, higher excretion of urinary potassium was found. There is evidence, that high salt intake might be associated with an increased arterial stiffness in humans and positive correlation of plasma sodium level with central PWV was found (Safar and Benetos 2003; Strauch *et al.* 2006). Changes in potassium balance may mediate some vascular effects of aldosterone, however aldosterone-mediated changes in potassium homeostasis do not appear to myocardial necrosis in experimental models (Martinez *et al.* 2002). Levels of urinary minerals excretion might be in relationship with central hemodynamics (Park *et al.* 2011). However, we found no correlation among plasma and urine minerals with PWV neither in PA, nor in EH group.

Significant differences in 24hour ABPM indices might attenuate our results, but the difference in central and peripheral PWV remained significant after adjustment for mean 24h BP. Furthermore, after multiple regression analysis, no relation among

24hour blood pressure indices and central and peripheral PWV was found in PA patients.

There are few other possible limitations of our study. No ultrasound or angiography was performed to exlude the presence of femoral atherosclerosis or stenosis in studied patients. However, only patients with no signs of peripheral arterial disease according to history and physical examination were included. Men and women are not represented equally in PA group. Thus, we tried to maintain the same distribution in EH group. Furthermore, the prevalence of menopause in women was similar in both groups, and no women with hormone replacement therapy were involved. In the time of investigation and at least two weeks prior to investigation (spironolactone was stopped six weeks before) patients were on comparable antihypertensive treatment. However, we could not be able to exclude the effect of former therapy on arterial stiffness, because structural vascular alteration modify in longer periods. Nevertheless, the number of antihypertensive drugs used before switching was slightly higher in PA groups, and the amount of patients with history of spironolactone use was comparable in both groups. Other possible limitation of our study is the relatively small amount of studied subjects. As we published recently (Somloova *et al.* 2010), different phenotype might be found in PA patients according to the subtype of PA (aldosterone producing adenoma / idiopathic bilateral hyperplasia), which was not distuingished in the current study. We would like to expand the number of subjects and continue to study certain subtypes of PA in the future and to evaluate the effects of treatment.

In conclusion, the present study demonstrates that aldosterone overproduction in PA does not preferentially affect the central arterial system. Both central and peripheral arterial stiffness were increased in PA compared to EH. Our data suggest

that RAAS might play role in peripheral PWV and plasma aldosterone seems to be important predictor of peripheral PWV in PA.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by research projects of the Ministry of Education of Czech Republic, Nos. 21620817 and 21620807 and by Charles University research project UNCE204010.

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Table 1. Clinical characteristics of studied subjects

	PA	EH	p-value
Sex (female/male)	49 (13 / 36)	49 (16 / 33)	- (0,512)
Age [years]	51±10	50±12	0,555
Duration of hypertension [years]	8 (2-14)	6 (2-12)	0,551
Body mass index [$kg.m^{-2}$]	29.7±4.3	30.1±4.6	0.674
Plasma sodium [mmol/l]	143±2	141±3	**0.008**
Plasma potassium [mmol/l]	3.7±0.4	4.1±0.4	**<0.001**
Creatinine [µmol/l]	79±15	80±17	0.814
Microalbuminuria [mg/l]	14 (8-35)	6 (4-10)	**<0.001**
eGFR [ml/min]	2.1±0.5	2.1±0.6	0.621
CC [$ml/s/1,73m^2$]	2.2±0.6	2.1±1.3	0.625
24-h urine sodium excretion [mmol/24h]	175±96	173±87	0.497
24-h urine potassium excretion [mmol/24h]	58±26	84±32	**<0.001**
Total plasma cholesterol [mmol/l]	4.9±0.9	4.8±1.1	0.690
LDL cholesterol [mmol/l]	3.0±0.8	2.9±0.9	0.459
HDL cholesterol [mmol/l]	1.2±0.3	1.2±0.3	0.626
Triacylglycerides [mmol/l]	1.3 (1.0-2.0)	1.4 (1.1-1.9)	0.710
Fasting plasma glucose [mmol/l]	5.2 (4.8-5.5)	5.1 (4.6-5.6)	0.434
Smokers, n (%)	22 (45)	15 (31)	-
Aldosterone [ng/dl]	37.8 (26.6-51.3)	13.2 (8.2-23.2)	**<0.001**
PRA [ng/ml/h]	0,51 (0,42-0,64)	0,88 (0,64-1,27)	**<0.001**
ARR [(ng/dl)/(ng/ml/h)]	74 (47-105)	18 (9-24)	**<0.001**

PA - patients with primary hyperaldosteronism; EH - essential hypertension patients; eGFR - estimated glomerular filtration rate; CC - creatinine clearance corrected for body surface area; LDL - low density lipoprotein; HDL - high density lipoprotein; PRA - plasma renin activity; ARR - aldosterone-to-renin-ratio

Values are shown as means±SD or medians (interquartile range) or absolute numbers and percentages. Variables are compared by unpaired t-test or Kruskal Wallis test where appropriate

Table 2. Hemodynamic parameters

	PA	EH	p-value
Clinical brachial SBP [mmHg]	154±18	150±16	0.317
Clinical brachial DBP [mmHg]	89±11	89±11	0.703
Brachial mean BP [mmHg]	111±13	110±11	0.481
Brachial pulse pressure [mmHg]	64±12	62±12	0.289
Heart rate [bpm]	68±10	68±12	0.837
24-h BP [mmHg]	146±15 / 88±10	139±13 / 84±11	**0.021** / 0.057
24-h heart rate [bpm]	68±8	69±10	0.633
Day BP [mmHg]	148±16 / 90±10	141±13 / 86±11	**0.033** / 0.060
Day heart rate [bpm]	71±8	72±10	0.659
Night BP [mmHg]	141±16 / 82±9	132±16 / 78±12	**0.009** / 0.054
Night heart rate [bpm]	61±8	61±9	0.851
Central Pulse wave velocity [m/s]	8,70±1,7	8,00±1,3	**0.023**
adjustment for clinical, 24h mean BP and age			**0.026**
Peripheral Pulse wave velocity [m/s]	11,59±1,4	10,70±1,3	**0.002**
adjustment for clinical, 24h mean BP and age			**0.018**

PA - patients with primary hyperaldosteronism; EH - essential hypertension patients; SBP - systolic blood pressure; DBP - diastolic blood pressure; BP - blood pressure

Values are shown as means±SD. Variables are compared by unpaired t-test. A multivariate regression model was used to adjust for between-group central and peripheral pulse wave velocity comparisons.

Table 3. Multiple regression analysis results

	β	p-value
Multiple regression analysis using PWV as dependent variable for EH		
Age [years]	0.623	**<0.001**
Pulse pressure [mmHg]	0.308	**0.004**
Multiple regression analysis using PWV as dependent variable for PA		
Age [years]	0.677	**<0.001**
Systolic blood pressure [mmHg]	0.455	**<0.001**
Multiple regression analysis using peripheral PWV as dependent variable for EH		
PRA [ng/ml/h]	0.400	**0.006**
24-h diastolic blood pressure [mmHg]	0.286	**0.049**
Multiple regression analysis using peripheral PWV as dependent variable for PA		
Aldosterone [ng/dl]	0.321	**0.030**

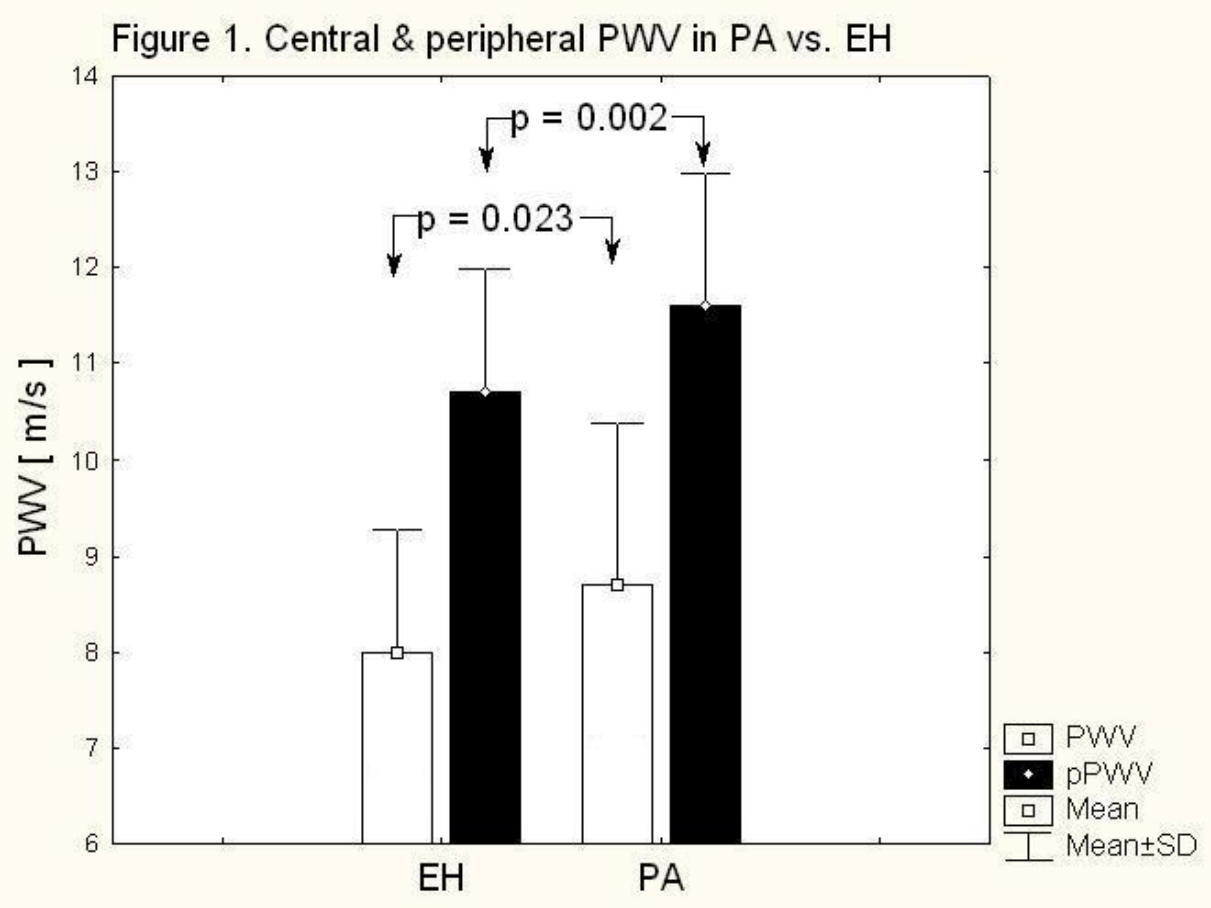
PWV - pulse wave velocity; PA - patients with primary hyperaldosteronism; EH - essential hypertension patients; PRA - plasma renin activity

β = multiple regression analysis coefficient

Table 4. Logistic regression analysis for PA as dependent variable and age, brachial mean BP, PWV, peripheral PWV as independent variable.

	Odds ratio	p-value
Age [years]	0.965	0.227
Brachial mean BP [mmHg]	0.973	0.205
PWV [m/s]	1.641	**0.033**
peripheral PWV [m/s]	1.725	**0.005**

PA - primary aldosteronism; EH - essential hypertension; BP - blood pressure; PWV - pulse wave velocity



Comparison of central and peripheral pulse wave velocity in primary aldosteronism and essential hypertension