Increased Arterial Wall Stiffness in Primary Aldosteronism in Comparison With Essential Hypertension

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Background: Aldosterone has been shown to substantially contribute to the accumulation of collagen fibers and growth factors in the arterial wall, which can increase wall stiffness. This study aimed at comparing arterial stiffness between patients with primary aldosteronism (PA), essential hypertension (EH), and normotensive controls using carotid–femoral pulse wave velocity (PWV) and central augmentation index (AI).

Methods: Thirty-six patients with confirmed PA, 28 patients with EH, and 20 normotensive subjects were investigated by Sphygmocor applanation tonometer.

Results: The office blood pressure (BP) at the time of the measurement (PA 167 ± 34/92 ± 12 mm Hg; EH 166 ± 19/91 ± 10 mm Hg), age, body mass index (BMI), cholesterol, triglyceride, blood glucose levels were comparable between PA and EH groups. The patients with PA had significantly higher PWV than the EH patients and control subjects (9.8 ± 2.6 m/sec *v* 7.5 ± 1.0 m/sec *v* 5.9 ± 0.7 m/sec, respectively; all mutual differences $P < .001$). The difference in PWV between PA and EH remained statistically significant also after the adjustment for all clinical variables including 24-h BP using multivariate analysis ($P = .001$).

Conclusions: Arterial wall stiffness is independently increased in PA compared to EH. This could be caused by the deleterious effects of aldosterone excess (potentially modulated by hypernatremia) on the fibrosis and remodeling of the arterial wall. Am J Hypertens 2006;19: 909–914 © 2006 American Journal of Hypertension, Ltd.

Key Words: Primary aldosteronism, aldosterone, arterial wall stiffness.

Primary aldosteronism (PA) is a secondary, endocrine-mediated form of hypertension defined by an autonomous aldosterone overproduction, which is caused in most cases by adrenocortical adenoma or bilateral adrenal hyperplasia. Recently published studies from various geographic populations reported significantly higher prevalence of PA in hypertensive patients (ranging from 5% to 30%) than the previously accepted data.[1,2] We have shown that PA is the most frequent form of endocrine hypertension in the Central Europe region (Czech Republic) with a considerably high (19%) prevalence in moderate-to-severe hypertension.[3]

Aldosterone is known to cause changes in arteriolar vasoactive tone and sodium homeostasis. Recent studies in vascular smooth muscle cell cultures and animal experiments demonstrated that aldosterone contributed substantially to the accumulation of collagen fibers and growth factors.[4,5] The role of aldosterone in the changes of aortic collagen accumulation using different pharmacologic interventions was also determined. One study indicated that the aldosterone antagonist spironolactone prevented the development of aortic fibrosis in spontaneously hypertensive rats.[6] In another study aldosterone administered to uninephrectomized Sprague-Dawley rats fed a high sodium diet increased carotid arterial stiffness in association with aortic fibronectin accumulation. This effect was independent of the wall stress, as shown by comparison with normotensive controls.[7] The aldosterone antagonist eplerenone reversed these vascular changes.[7]

There are only few data dealing with the aldosterone effect on vascular changes in humans.[8,9] The study on essential hypertension has shown that the treatment with

Received November 11, 2005. First decision February 3, 2006. Accepted February 6, 2006.

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This study was supported by grant No. NR 8155-5 from the Ministry of Health of the Czech Republic and Grants from the Ministry of Education, Youth and Sports MSM 0021620817 and MSM 0021620807.

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0895-7061/06/$32.00
doi:10.1016/j.amjhyper.2006.02.002

the aldosterone antagonist spironolactone is able to reduce significantly the augmentation index (AI) and pulse wave velocity (PWV).[9] The investigators also found positive correlations between the aldosterone-to-renin ratio (ARR) and AI, but not between ARR and PWV. Patients with PA are at greater cardiovascular risk than patients with EH.[10] However, no data exist on the arterial wall stiffness as a cardiovascular risk factor in patients with PA.

The presents study aimed at comparing arterial stiffness between patients with PA, essential hypertension (EH), and normotensive controls by use of central aortic AI (derived from the radial artery pulse wave) and carotid–femoral PWV. Specifically, we investigated the hypothesis that arterial stiffness is increased in patients with PA when compared to EH patients independently of other clinical variables.

Methods

Study Population

We studied 36 patients with confirmed PA (19 men, aged 52 ± 11 years), 17 with aldosterone-producing adenoma confirmed by surgery, 4 with idiopathic aldosteronism, and 15 with an unclassified form (refusal of further investigation or unsuccessful adrenal venous sampling); 28 patients with EH (13 men, aged 49 ± 9 years); and 20 healthy normotensive controls (12 men, aged 46 ± 11 years).

The patients with PA and EH discontinued their usual antihypertensive therapy and were switched to an α-blocker (doxazosine) or slow release verapamil for at least 14 days before the investigation to eliminate the interference of other antihypertensive drugs with the renin-angiotensin-aldosterone system.

Laboratory Tests

The screening for the diagnosis of PA was based on an elevated ARR $\geq$50 [(ng/100 mL)/(ng/mL/h)][3] when plasma renin activity (PRA) and aldosterone levels were measured after 2 h of upright position, suppressed PRA ($\leq$0.7 ng/mL/h), and elevated plasma aldosterone ($\geq$150 ng/L). The diagnosis of PA was confirmed by the absence of plasma aldosterone suppression after saline infusion (plasma aldosterone $\leq$ 80 ng/L), as previously described,[11] and by the histologic findings in patients with aldosterone-producing adenoma. The diagnosis of EH was made by the exclusion of all forms of secondary hypertension. All hormonal tests were performed by radioimmunoanalysis using commercially available kits. Other biochemical parameters were analyzed at the institutional central laboratory.

Pulse Wave Analysis

All subjects were studied after an overnight fasting in a quiet room. After 15 min of rest in the supine position, the pulse wave analysis and PWV measurements were performed by the applanation tonometer SphygmoCor (AtCor Medical, West Ryde, Australia).

Pulse wave was measured at the radial artery and the aortic pulse wave was derived by means of generalized transfer function. The aortic waveform was calibrated using a single simultaneous measurement of brachial artery blood pressure (BP) by oscillometric sphygmomanometer (Dinamap, Critikon, Tampa, FL). The aortic (or central) AI was calculated as the ratio of the pressure difference (ΔP) between the shoulder of the wave and the peak systolic pressure according to the formula AI = (ΔP/systolic BP $-$ diastolic BP) $\times$ 100.[12] The AI values were corrected for differences in heart rate from 75 beats/min using a SphygmoCor built-in algorithm.[12] In a previous large study, the generalized transfer function used by SphygmoCor provided an acceptable estimate of the ascending aortic systolic, diastolic, and pulse pressures under different conditions.[13] A high level of repeatability and reproducibility of SphygmoCor pulse wave measurements has been established for various patient groups.[14,15]

Aortic PWV was assessed by the time difference between pulse wave upstrokes, which were consecutively measured at the right carotid artery and right femoral artery and aligned by electrocardiogram (ECG)-based trigger. The "percentage pulse height algorithm" was used to locate the "foot" of the pulse waves.

The oscillometric Spacelabs 90207 device (Spacelabs Medical, Redmond, WA) was used for 24-h ambulatory BP monitoring.

Statistical Analysis

Data were described by mean ± standard deviation (SD). Continuous variables with clearly non-normal distributions (Shapiro-Wilks W test) were described as medians (interquartile range). Individual patient groups were compared by two-tailed t test for independent samples or Kruskal-Wallis test when appropriate. The χ^2 test with Yates correction was used for categorical variables. Pearson's correlation analysis was performed to characterize the inter-relationship between individual variables. Non-normally distributed variables were log-transformed before this analysis. Analysis of covariance (ANCOVA) and multivariate linear regression models were used when appropriate to correct for the differences in clinical and biochemical characteristics. $P < .05$ was considered significant.

Results

The basic characteristics of the groups are shown in Table 1. The duration of hypertension was comparable in both hypertensive groups (EH: 11 ± 10 years, PA: 12.6 ± 10 years). The proportion of smokers was as follows: 3 smokers and 8 ex-smokers in the PA group, 11 smokers and 5 ex-smokers in the EH group, and 3 smokers in the control group.

Table 1. Characteristics of studied subjects

	Primary Aldosteronism	Essential Hypertension	Controls
Number of subjects	36	28	20
Age (years)	52 ± 11#	49 ± 9	46 ± 11
Duration of hypertension (years)	12.6 ± 10.0	11.0 ± 10.0	—
Body mass index (kg/m^2)	27.7 ± 4.9	28.1 ± 4.2§	25.3 ± 3.7
Plasma cholesterol (mmol/L)	4.9 ± 1.2	5.1 ± 1.0	5.3 ± 1.0
LDL-cholesterol (mmol/L)	2.8 ± 1.0	2.9 ± 0.8	3.1 ± 0.7
HDL-cholesterol (mmol/L)	1.4 ± 1.0	1.4 ± 0.4	1.68 ± 0.47
Fasting plasma glucose (mmol/L)[a]	5.0 (4.55;5.25)	4.9 (4.45;5.40)	4.8 (4.5;5.1)
Plasma aldosterone—upright (ng/L)[a]	355 (268;738)	106 (92;181)	—
Plasma renin activity—upright (ng/mL/h)[a]	0.31 (0.24;0.55)**	1.17 (0.63;1.86)	—
Aldosterone/renin ratio—upright (ng/100mL)/(ng/mL/h)[a]	105.11 (78;232)**	12 (6;18)	—
Plasma potassium (mmol/L)	3.3 ± 0.5**##	4.1 ± 0.4	4.3 ± 0.3
Plasma sodium (mmol/L)	144.6 ± 2.8**	142.4 ± 3.1	—
Urine sodium (mmol/24 h)	155 ± 81*	117 ± 58	—
Urine potassium (mmol/24 h)	102 ± 60**	55 ± 23	—

Data are shown as means ± SD and compared by two-tailed t-test for independent samples. Variables with clearly non-normal distributions ([a]) are shown as medians (interquartile range) and compared by Kruskal-Wallis test.

PA versus EH * $P < .05$, ** $P < 0.001$; PA versus controls # $P < 0.05$, ## $P < 0.001$; EH versus controls § $P < 0.05$.

Patients in PA group were somewhat older than controls and EH patients had slightly higher body mass index (BMI) than controls. There were not significant differences in age, duration of hypertension, lipid profile, and glucose between EH and PA groups. As expected, patients with PA had significantly lower plasma potassium, PRA, and higher aldosterone, aldosterone-to-renin ratio, and plasma sodium concentrations.

Directly measured and derived central BP indices together with the results of pulse wave analysis are summarized in Table 2. The office BP at the time of the investigation was comparable between both hypertensive groups. Similarly, no significant differences were found for heart rate and derived aortic BP. However, PA patients had significantly higher mean 24-h ambulatory BP than EH. Both EH and PA patients had a significantly higher AI (but mutually not significantly different) when compared to normotensive controls. On the contrary, patients with PA had significantly higher PWV than EH patients and control subjects (9.8 ± 2.6 m/sec *v* 7.5 ± 1.0 m/sec *v* 5.9 ± 0.7 m/sec, respectively; all mutual differences $P < .001$).

The difference in PWV between PA and EH remained statistically significant even after the adjustment for individual clinical (gender, age, duration of hypertension, office and ambulatory systolic and diastolic BP, BMI, and heart rate) and biochemical variables (serum total, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, sodium, and potassium concentrations). The diagnosis (EH

Table 2. Blood pressure and pulse wave indices

	Primary Aldosteronism	Essential Hypertension	Controls
Office brachial SBP (mm Hg)	167 ± 34‡	166 ± 19#	119 ± 11
Office brachial DBP (mm Hg)	92 ± 12‡	91 ± 10#	71 ± 8
Brachial pulse pressure (mm Hg)	75 ± 18‡	76 ± 16#	49 ± 7
Central SBP (mm Hg)	152 ± 25‡	151 ± 21#	106 ± 10
Central DBP (mm Hg)	92 ± 11‡	92 ± 11#	71 ± 7
Central pulse pressure (mm Hg)	59 ± 17‡	59 ± 16#	35 ± 6
Mean 24-h SBP (mm Hg)	153 ± 17*	139 ± 15	—
Mean 24-h DBP (mm Hg)	93 ± 11*	87 ± 10	—
Heart rate (beats/min)	68 ± 11	69 ± 11	67 ± 10
Augmentation index (AI) (%)	28 ± 10‡	27 ± 14§	18 ± 14
AI adjusted for heart rate of 75 beats/min (%)	26 ± 9‡	25 ± 15§§	13 ± 14
Pulse wave velocity (m/s)	9.8 ± 2.5**‡	7.5 ± 1#	5.9 ± 0.7

Values are shown as means ± SD.

SBP = systolic blood pressure; DBP = diastolic blood pressure.

Two-tailed t-test for independent samples: PA versus EH * $P < 0.01$, ** $P < 0.001$; PA versus controls ‡ $P < 0.001$; EH vs controls § $P < 0.05$, §§ $P < 0.01$, # $P < 0.001$.

Table 3. Correlations between indices of arterial stiffness and clinical/biochemical parameters

	Primary Aldosteronism		Essential Hypertension	
	PWV	**AI^{75}**	**PWV**	**AI^{75}**
Age	$r = 0.61$; $P < .001$	$r = -0.06$; $P =$ ns	$r = 0.41$; $P < .05$	$r = 0.27$; $P =$ ns
Brachial SBP	$r = 0.52$; $P = .001$	$r = 0.36$; $P < .05$	$r = 0.25$; $P =$ ns	$r = 0.18$; $P =$ ns
Brachial DBP	$r = 0.21$; $P =$ ns	$r = 0.45$; $P < .01$	$r = 0.2$; $P =$ ns	$r = 0.34$; $P = .07$
Plasma sodium	$r = 0.45$; $P < .01$	$r = 0.12$; $P =$ ns	$r = 0.26$; $P =$ ns	$r = -0.07$; $P =$ ns
Plasma potassium	$r = -0.03$; $P =$ ns	$r = 0.14$; $P =$ ns	$r = 0.05$; $P =$ ns	$r = -0.39$; $P < .05$

r = Pearsons correlation coefficient; PWV = pulse wave velocity; AI^{75} = augmentation index adjusted for heart rate 75/min; other abbreviations as in Table 2.

versus PA) was the only significant variable that was associated with PWV when all clinical variables were simultaneously entered into the multiple linear regression model. Moreover, the diagnosis remained the significant determinant of PWV ($P = .009$) in the regression model, which included fundamental biochemical features of PA (aldosterone-to-renin ratio, plasma potassium and sodium levels).

The PWV moderately correlated with age and office systolic BP in PA patients, whereas this correlation was weak in EH patients (Table 3). Fig. 1 illustrates the positive correlation between systolic BP and PWV in the PA group in contrast to the EH patients. Divergent regression lines for both hypertensive groups suggest a systolic BP-independent discriminative power of PWV. Correlations between AI, age, and BP were only modest and of borderline significance in individual analyses. We did not find any relationship between indices of arterial stiffness and hormone levels in both PA and EH groups. We observed a significant correlation between plasma sodium and PWV in PA, but not in the EH group (Table 3). The values of urinary sodium and potassium excretion/24 h, plasma aldosterone, PRA, and ARR were not correlated with PWV or AI.

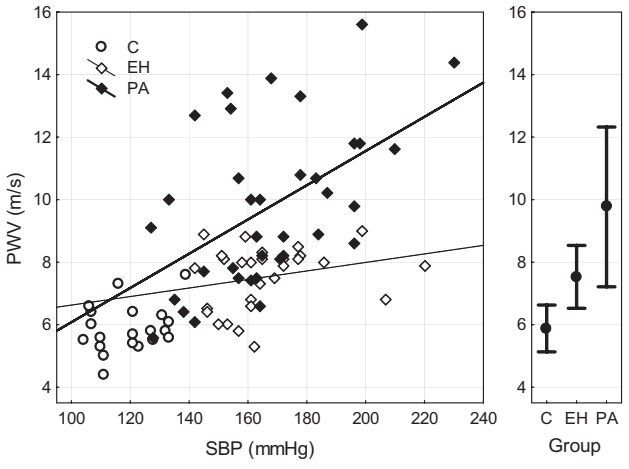

FIG. 1. Relationship between pulse wave velocity (PWV) and systolic blood pressure (SBP) in studied groups. (**Left**) Note the steeper slope of regression line for PA (**thick line**) compared to EH patients (**thin line**) suggesting SBP-independent discriminative power of PWV. C = controls, open circles; EH = essential hypertension, open diamonds; PA = primary aldosteronism, solid diamonds. (**Right**) Whisker plot of PWV (mean and standard deviation) categorized by studied groups.

Discussion

This study demonstrated that hypertensive patients have higher arterial stiffness (according to PWV) than healthy controls. This observation might be, however, simply due to the hypertension per se rather than due to genuine changes in arterial wall properties. Therefore, the major finding of our study is that PA patients have higher arterial stiffness even when compared to EH patients and that this difference is independent of all clinical characteristics, in particular office BP and global hypertension burden measured by 24-h ambulatory BP monitoring. Our results thus indicate more profound arterial wall damage in patients with PA in comparison with patients with EH. This observation supports the earlier findings of increased aortic stiffness in rats given aldosterone and a high salt diet.[7]

Gender has been shown to influence vascular compliance in hypertensives and normotensives.[16] We have not observed any significant gender differences in studied groups. In addition, higher PWV in PA compared to EH remained significant even if gender was entered into the multivariate regression model.

Surprisingly, we did not find significant differences in the AI between PA and EH. Several suggestions can be made. The difference between PA and EH may in fact be due to the predominant changes in the central parts of the arterial tree. The AI is a complex index describing mainly wave reflections occurring at the branching of the arterioles. Consequently, AI seems to be more influenced by different confounding factors like age, height, gender, BP, and vasoactive drugs than the PWV.[17] Furthermore, AI assessment is more operator-dependent and less robust than PWV measurement. Although linear relationship between PWV and AI was repeatedly found,[17] some investigators reported a weaker correlation and considered PWV to be a more precise marker of central vessels stiffness.[18]

The hormonal effect of aldosterone overproduction on

vascular changes might contribute to the observed differences in PWV between PA and EH. Close and inverse correlation between systemic arterial compliance and the plasma aldosterone concentration was reported in essential hypertensives, but not in normotensives.[19] An inverse relationship between aldosterone and large artery compliance was also found in chronically treated patients with heart failure.[20] No significant correlation was, however, found between hormonal levels (PRA, aldosterone) and arterial stiffness indices in our study. These results are similar to the findings of another study, where the researchers reported the absence of a direct relation between vascular stiffness and plasma aldosterone.[21] Two explanations can be proposed. First, hormone levels assessed during investigation (drug washout period) may not correspond to chronic impact of hyperaldosteronism before the diagnosis of PA. Second, plasma aldosterone levels may not reflect the local production of aldosterone in the vascular wall. This hypothesis is further supported by the finding of a 17-fold higher concentration of aldosterone in cardiac tissue compared to plasma.[22]

Our data support also the possibility that increased PWV in PA might be modulated by higher plasma sodium concentrations, as we found a significant positive correlation between PWV and serum sodium concentration. Previous studies demonstrated that high salt intake is associated with an increased arterial stiffness in humans.[23] In addition, sodium intake seems to modulate the effect of aldosterone synthase polymorphism (CYP11B2 C-344T) on arterial stiffness.[21] The PA patients had significantly higher natriuresis than patients with EH, as no rigorous dietary measures were implemented during short period of hospital investigation. However, no significant correlation was found between natriuresis and serum sodium concentration, and between natriuresis and PWV in PA patients. Therefore, we believe that elevated serum sodium concentration per se (due to aldosterone overproduction) is, at least in part, responsible for the increased PWV.

It has been suggested that potassium might exert vascular protective effects.[24,25] Despite expected differences in plasma potassium concentrations we did not find, however, any convincing impact of this variable on PWV (Table 3). The design of our cross-sectional study does not allow the speculation about this specific potassium effect.

Our study has a possible limitation in the relatively smaller sample size (36 PA, 28 EH, 20 controls), which was caused by our effort to find the comparable hypertensive populations (age, duration of hypertension).

In conclusion, patients with PA have increased aortic wall stiffness when compared to EH patients, even after the adjustment for incidental between-group differences. This finding could be caused by the deleterious effects of aldosterone excess (potentially modulated by hypernatremia) on the fibrosis and remodeling of the arterial wall. This observation is in agreement with the increased cardiovascular risk in PA in comparison with EH patients.

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