CLINICAL STUDY

Relationship between plasma aldosterone and left ventricular structure and function in patients with essential hypertension

Lazurova I, Valocik G, Zabranska B, Fraenkel E

2nd Department of Internal Medicine, Faculty of Medicine, Safarikiensis University, Kosice, Slovakia. **lazurova@central.medic.upjs.sk**

Abstract

Recent experimental studies demonstrated that elevation of plasma aldosterone is associated with an increased collagen accumulation resulting in myocardial fibrosis.
The aim of this study was to evaluate the association of circulating aldosterone with cardiac structural and functional changes in patients with essential hypertension. The authors examined 39 patients (aged 51±14 years, 13 male, 26 female) with essential hypertension. M-mode and two-dimensional echocardiography was performed in each subject. Plasma renin activity (PRA) and plasma aldosterone (PA) at baseline and after 4 hours upright posture were measured.
Mean levels of baseline and stimulated PRA were similar in hypertensives and control group of normotensives. Baseline and stimulated PA levels were mildly but not significantly higher compared to control group. Using Tukey Kramer multiple analysis we found a significant positive correlation of both baseline and stimulated PA with echocardiographic parameters of left ventricle in hypertensive subjects: IVSd ($p<0.001$), PWd ($p<0.001$), LVIDd ($p<0.001$) and E/A ($p<0.001$). However, no correlation between PRA and left ventricular structure and function was found in this group of patients.
The authors conclude that plasma aldosterone levels are related to the structure and function of left ventricle. (Tab. 3, Ref. 20.)
Key words: aldosterone, myocardial fibrosis, left ventricle.

Since the demonstration of mineralocorticoid receptors and the enzyme 11-hydroxysteroid dehydrogenase in the heart, recent observations have led to a reconsideration of the role of aldosterone in the pathogenesis of cardiovascular diseases (Lombes et al, 1995).In addition to its classical effects (i.e. fluid and sodium retention, and potassium excretion), aldosterone exerts direct effects on the myocardium. It promotes the development of fibrosis in hypertrophied cardiac ventricles, reduces myocardial perfusion and increases the incidence of cardiovascular events (Weber et al, 1995).Recent experimental studies demonstrated that elevation of plasma aldosterone is associated with an increased collagen accumulation, resulting in myocardial fibrosis (Brilla et al, 1995). Moreover, some clinical studies showed a significant relationship between plasma aldosterone and echocardiographic parameters of the left ventricle, such as left ventricular size and mass, cardiac index and E wave/A wave time-velocity integral ratio (Rossi et al, 1998; Schlaich et al, 2000). In essential hypertension, aldosterone can contribute to hypertension and increases the incidence of myocardial hypertrophy and cardiovascular events. It causes autonomic imbalance, electrolyte abnormalities, contributing to myocardial dysfunction, arrhythmias and sudden cardiac death (Struthers, 2002). On the other hand inhibition of renin–angiotensin–aldosterone is associated with a decrease in blood pressure and regression of left ventricular hypertrophy (Suzuki et al, 2002).The aim of this study was to evaluate the relationship of circulating aldosterone with cardiac structural and functional changes in patients with essential hypertension.

Subjects and methods

The study group comprised 25 normotensives (control group) and 39 patients aged 51±14 years (13 male, 26 female) with mild essential hypertension (World Heart Organisation stages I to II).

2nd Department of Internal Medicine, Faculty of Medicine, Safarikiensis University, Kosice

Address for correspondence: I. Lazurova, MD, PhD, 2nd Dept of Internal Medicine, LF UPJS, Trieda SNP 1, SK-040 01 Kosice, Slovakia. Phone: +421.55.6423444

Secondary types of hypertension had to be ruled out by thorough clinical and laboratory evaluation.

Two-dimensional-guided M-mode echocardiography was performed in each subject using a 2.5 MHz probe (Esaote Biomedica). The interventricular septal thickness in end-diastole (IVSd), posterior wall thickness in end-diastole (PWd), left ventricular internal dimension in end-diastole (LVIDd) and E wave/A wave ratio were used for analysis. 10 patients with essential hypertension had septal thickness (i.e. more than 12mmIVSd).

Blood samples for the investigation of plasma renin activity (PRA) and plasma aldosterone (PA) were collected in the supine position at 7.00 o'clock (baseline) and after 4-hours of upright posture at the diet with normal saline content (100–150 mEq/d).

PRA was measured by angiotensin I radioimmunoassay (kit Immunotech, Prague, Czech Republic) and plasma aldosterone using radioimmunoassay kit Immunotech France.

Statistical analysis was performed using the Tukey-Kramer multiple comparisons test.

Results

Mean levels of the supine and upright plasma renin activity (PRA) are shown in table 1 and the data were similar in both hypertensives and normotensives. Values of supine PRA were not statisticaly different between patients and the control group (1.28±0.6 ng/ml/h vs 1.3±0.3 ng/ml/h). Upright PRA was mildly but not significantly higher in the hypertensives compared to normotensives (4.1±0.95 vs 2.4±0.4 ng/ml/h).

There were no significant differences in supine (54±16 vs 62.6±11 pg/ml) and upright plasma aldosterone values (169±28 vs 136±16 pg/ml) between patients with essential hypertension and the control group of normotensive subjects (Tab. 1).

There was a positive correlation between supine PA and echocardiographic parameters of the left ventricle: IVSd ($p<0.001$), pWd ($p<0.001$), LVIDd ($p<0.001$) and E wave/A wave ratio ($p<0.001$) (Tab. 2).

A significant positive correlation was detected between echocardiographic parameters and upright PA as well (Tab. 2). No correlation between these parameters was observed in normal subjects, i.e. normotensivess. There was no significant correlation between baseline and upright PRA and left ventricular structure and function in this group of patients.

Tab. 1. Echocardiographic parameters of the left ventricle and values of PRA and PA in patients with essential hypertension (n=39) and the control group of normotensives (n=25).

Parameter	Normotensives	Hypertensives
supine PRA (ng/ml/h)	1.3 ± 0.3	1.28 ± 0.6
upright PRA (ng/ml/h)	2.4 ± 0.4	4.1 ± 0.95
supine PA (pg/ml)	54 ± 16	62.6 ± 11
upright PA (pg/ml)	169 ± 28	136 ± 16
IVSd (cm)	0.9 ± 0.2	1.17 ± 0.23
PWd (cm)	0.9 ± 0.3	1.08 ± 0.056
LVIDd (cm)	4.7 ± 0.9	4.86 ± 0.08

Tab. 2. Correlations between echocardiographic parameters and plasma aldosterone in patients with essential hypertension (n=39).

Parameters	Significance of correlation
supine PA vs IVSd	$p<0.001$
supine PA vs LVIDd	$p<0.001$
supine PA vs PWd	$p<0.001$
supine PA vs E/A	$p<0.001$
upright PA vs IVSd	$p<0.001$
upright PA vs LVIDd	$p<0.001$
upright PA vs PWd	$p<0.001$
upright PA vs E/A	$p<0.001$

The baseline (61.7±7.4 pg/ml, vs 42.2±8 pg/ml, $p<0.05$) and upright plasma (169±24pg/ml vs 88.5±18 pg/ml, $p<0.01$) aldosterone was significantly higher in patients with septal thickness, i.e. IVSd>12 mm than those with IVSd<12 mm (Tab. 3). There were no significant differences in baseline and upright PRA between these groups.

Discussion

Until recently aldosterone was thought to contribute to the development of heart failure, essentially through an indirect pathway – increased renal sodium reabsorption that leads to volume expansion and hypervolemia. This concept was in accord with the known mineralocorticoid effects of aldosterone.

Recent observation have led to a reconsideration of the role of aldosterone in the development of heart failure because it was demonstrated that in addition to its classical effects, aldosterone can exert direct effects on the heart. Weber et al (1995) demonstrated that the hormone induces the development of fibrosis in hypertrophied cardiac ventricles independently of hemodynamic changes. This observations has been confirmed by others.

The existence of aldosterone receptors in the rabbit heart and their intramyocardial distribution were described in 1992 (Lombes et al, 1992). Bonvalet et al (1995) demonstrated that the mineralocorticoid receptor protective enzyme 11– dehydrogenase is specifically coexpressed with receptors in aldosterone target cells.

Thus, all the cellular components required for direct, selective aldosterone action are present in human cardiomyocytes.

Cardiac fibroblasts are known to have high affinity corticoid receptors for aldosterone and account for the accumulation of collagen within the interstitium of the rat myocardium in acquired and genetic hypertension (Brilla, 2000). The competitive aldosterone receptor antagonist, spironolactone, is able to prevent fibrosis in both ventricles (Brilla et al, 1993; Barr et al, 1995; Ramires et al, 2000).

Left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality. Experimental data have revaled that elevated circulating aldosterone is associated with collagen accumulation resulting in fibrosis in hypertrophied cardiac ventricles.Similarly, some authors documented in human

Tab. 3. Mean values of baseline and upright plasma aldosterone and PRA in group with and without septal wall thickness.

	IVSd<12	IVSd>12	p
PA supine (pg/ml)	42.2±8	61.7±7.4	0.05
PA upright (pg/ml)	88.5±18	169±24	0.01
PRA supine (ng/ml/h)	1.13±0.5	1.32±0.7	NS
PRA upright (ng/ml/h)	3.86±1.1	4.26±0.9	NS

studies that aldosterone displayed a close correlation with structural and hemodynamic parameters of the left ventricle (Zannad et al, 1995; Schlaich et al, 2000).

Tanabe et al found that left ventricular hypertrophy is more prominent in patients with primary aldosteronism than in patients with other types of secondary hypertension (Tanabe et al, 1997).

In the study of Rossi et al (1998) patients with primary aldosteronism had a significantly higher cardiac index and lower E/A wave time velocity integral ratios.

In various studies with essential hypertension there was a significant correlation between plasma aldosterone and septal, posterior and relative wall thickness. On the other hand, patients with hypertension and pathologic patterns of left ventricular geometry were characterized by elevation of aldosterone (Muscholl et al, 1998). Additionally, spironolactone improves left ventricular volume and mass as well as decreases the levels of brain natriuretic peptide (BNP), a biochemical marker of prognosis or left ventricular hypertrophy (Tsutamoto et al, 2001).

In the present study we examined the association between plasma aldosterone, concentration and LV structure and function ina control group of normotensive subjects and a group of patients with essential hypertension stage I-II (WHO/ISH). Our results indicate that elevation of plasma aldosterone is related to left ventricular mass and function, because plasma aldosterone levels correlated with IVSd, PWd, LVIDd and E/A ratio. However we were not able to demonstrate a relationship between plasma renin activity and echocardiographic parametrs of the left ventricle, which was documented in previous studies. Systemic renin seems not to be involved in left ventricle remodelling, but it is possible that the local renin-angiotensin system plays another role, which was not evaluated in this study.

We did not find a difference in PRA and aldosterone between normotensives and hypertensives. According to some authors, essential hypertension can be devided into three groups – low, normal and high renin essential hypertension. There were all three groups of patients in our study, so that the mean PRA and aldosterone were not different compared to normal subjects.

The importance of nonhemodynamic (humoral) factors in cardiac hypertrophy in humans has been shown by Duprez et al (1993). They found that left ventricular mass correlated with plasma aldosterone levels independently of blood pressure. They found significantly higher PA levels in patients with septal wall thickness (IVSd more than 12 mm) than those with normal septal wall. This is in agreement with some previous studies, however, Iwashima et al (2002) documented that PAC was significantly higher only in patients with eccentric hypertrophy than in those with concentric hypertrophy, but this was not followed up in this study.

In agreement with these results, our data indicate that aldosterone is involved in structural and functional changes of the human heart in patients with essential hypertension.

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