The role of aldosterone in myocardial dysfunction of Egyptian patients with essential hypertension

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Abstract

Introduction: Aldosterone is a potent mineralocorticoid. It plays a key role in mediating adverse myocardial remodeling with pressure overload. The aims of this study were to compare the serum levels of aldosterone in well controlled and uncontrolled cases of long standing essential hypertension and correlate these levels to the echocardiographic findings of these patients.
Material and methods: Eighty subjects were enrolled in the study: 30 well controlled hypertensives, 30 uncontrolled hypertensives and 20 subjects matched for age and sex as a control group.
Results: There was a significant elevation of serum aldosterone level in hypertensive patients which was especially marked in uncontrolled hypertensives compared to the control group. There was a significant positive correlation between aldosterone level and hypertension duration, mean systolic and mean diastolic blood pressure. There was a significant positive correlation between aldosterone level and posterior wall thickness in well-controlled hypertensives and a significant correlation with posterior wall thickness in uncontrolled hypertensives. Aldosterone levels were significantly significant correlated with septal wall thickness only in uncontrolled hypertensives. A significant negative correlation between aldosterone level and fractional shortening percentage, ejection fraction percentage and E/A ratio of left ventricle in controlled and uncontrolled hypertensives was demonstrated. Aldosterone level increase was associated with hypertrophic changes, relative impairment of systolic functions and disturbed diastolic functions that were more significant in uncontrolled hypertensives.
Conclusions: Aldosterone receptor blockers should be considered, in the treatment of hypertension to avoid the adverse effects of remodeling on systolic and diastolic function of left ventricle.

Key words: aldosterone, hypertension.

Introduction

Aldosterone is a potent mineralocorticoid that promotes sodium retention and elevation of arterial pressure [1]. Within the myocardium aldosterone acts via mineralocorticoid receptors to enhance extra cellular matrix and collagen deposition. Independent of its effect on blood pressure, aldosterone may also play an important role in cardiac hypertrophy [2].

The two key pathological processes in left ventricular hypertrophy (LVH) are hypertrophy of the myocyte and fibrosis of the interstitium. The fibrosis occurs as a result of an increase in the extra cellular matrix and more specifically from an increase in the concentration of collagen type I and III

[3]. There is primary fibrosis as well as secondary reparative fibrosis following myocyte necrosis [4]. The cumulative end effect is distortion of tissue structure and an increase in myocardial stiffness, which has a pathological significance in the development of diastolic dysfunction, as a substrate for ventricular arrhythmia and ultimately in the development of systolic dysfunction [5].

Although, left ventricular hypertrophy may cause clinical heart failure due to diastolic dysfunction, progressive adverse remodeling may also lead to ventricular dilatation, pump failure a consequent poor prognosis [6].

Recent studies have shown that aldosterone probably acting through mineralocorticoid receptors can induce apoptosis [7]. Chronic pressure overload due to hypertension is a major cause of heart failure [6]. Pressure overload leads to increased myocyte apoptosis that may contribute to myocardial failure. Myocardial failure is associated with apoptotic death of cardiac myocytes and degradation of the interstitium matrix [8].

In addition, it has been shown that activation of matrix metalloproteinase (MMP), which degrade most components of the interstitial matrix, precedes left ventricular dilatation in high salt hypertension [9]. Mineralocorticoid receptors affect MMP activity while angiotensin converting enzyme (ACE) inhibition suppresses MMP activation and prevents left ventricular remodeling and dysfunction [10].

Thus it is possible that aldosterone, acting via mineralocorticoid receptors, is involved in mediating at least some of the cellular events observed in pressure overload induced myocardial failure [11].

The aims of this study were to compare the serum levels of aldosterone in well controlled and uncontrolled patient with essential hypertension and correlate these levels to echocardiographic findings in these patients.

Material and methods

Eighty subjects were prospectively enrolled into this study which was approved by the local ethical committee. They were divided into three groups; group (A) consisted of thirty patients with history of controlled essential hypertension as a result of effective treatment in the form of diuretics, angiotensin converting enzyme inhibitors or both but not aldosterone inhibitors with a duration of hypertension ranging from between ten and fifteen years, group (B) consisted of thirty patients with history of uncontrolled essential hypertension who had either ineffective or neglected treatment and group (C) which consisted of twenty control patients who had no history of hypertension (normotensive) and were matched for age and sex.

Controlled hypertension was defined as blood pressure <140/90 mm Hg while uncontrolled hypertension was defined as blood pressure ≥140/90 mm Hg. The blood pressure was measured three times on three successive days under the same conditions to confirm the diagnosis.

Exclusion criteria were: diabetes mellitus, dyslipidemic patients, patients with renal impairment, patients with congenital, rheumatic or ischaemic heart disease as proven by clinical examination, resting twelve leads ECG or echo Doppler study. All exclusion criteria were chosen due to their potential effect on cardiac function.

Five milliliters of venous fasting blood (overnight fasting) was taken from each subject participating in the study. Samples were taken after thirty minutes of lying down and divided into two aliquots, the first was left to clot. Serum after separation was stored at –70°C for determination of serum aldosterone by radio immunoassay [12]. The second aliquot was placed in EDTA and centrifuged at room temperature then frozen immediately at –70°C for determination of plasma rennin activity (PRA) by radio immunoassay [13]. Both kits were supplied from Dia Sorin (Stillwater, Minnesota, 55082-0285, USA).

The three groups of patient had echocardiography Doppler studies to assess systolic and diastolic functions by transthoracic resting study using 3.5 mega hertz transducer and Sigma 44 echo Doppler machine.

Combined two dimensional short axis view and M mode examination from left lower parasternal position view were used to measure left ventricular end diastolic diameter and end systolic diameter from leading edge to leading edge as according to American Heart Association instructions.

Fractional shortening percentage was calculated according to the formula:

$$\text{FS\%} = \frac{\text{LV EDD} - \text{LV ESD} \times 100}{\text{LV EDD}}$$

Ejection fraction was calculated according to the formula:

$$\text{EF\%} = \frac{\text{LV EDV} - \text{LV ESV} \times 100}{\text{LV EDV}}$$

Left ventricular inflow pattern was detected using combined two-dimensional four-chamber view and pulsed wave Doppler examination from apical position at the mitral valve level. Additionally we measured: E wave (velocity at early mitral inflow) A wave (velocity of mitral inflow at atrial systole) and E/A ratio [14].

Statistical analysis

Results were expressed as mean ± SD. Data was statistically analyzed using SPSS package for Windows, version 7.5. One-way analysis of variance was used when the means of more two variables were being compared. A correlation matrix test was used to study the relationship between two continuous variables. Student t-test was used to compare two means and Chi-square test was used to compare frequency between two categorical variables.

Results

The study demonstrated an elevation of serum aldosterone level in hypertensive patients in both controlled and uncontrolled hypertensive groups compared to the control group. This elevation was more significant in the uncontrolled group (P<0.05). Similar findings were observed with plasma rennin activity (PRA) (Table I).

Compared to the control group echocardiography of the well controlled hypertensive group revealed a significant increase in left ventricular wall thickness (P<0.05), an insignificant increase in septal wall thickness (P>0.05), a significant decrease in fractional shortening % (P<0.05), a significant decrease of ejection fraction % (P<0.05), and a highly significant decrease in E/A ratio (P<0.001) (Table II).

Compared to the control group echocardiography of the uncontrolled hypertensive group revealed a significant increase in the left ventricular posterior wall thickness (P<0.001), a significant increase in septal wall thickness (P<0.05), a highly significant decrease in fractional shortening (P<0.001) and a highly significant decrease in E/A ratio (P<0.001) (Table III).

Compared the control group the well controlled hypertensive group showed a significant increase in post wall thickness and septal wall thickness (P<0.05), a significant reduction in fractional shortening (P<0.05), a highly significant reduction in ejection fraction (P<0.001) and a significant reduction in E/A ratio (P<0.05).

In the well controlled hypertensive group (A) there was a non significant correlation (P>0.05) between serum aldosterone level, age, sex and septal wall thickness. There was a significant positive correlation (P<0.05) between serum aldosterone level, duration of hypertension, mean systolic blood pressure, mean diastolic blood pressure, serum plasma rennin activity and posterior left ventricular wall thickness. However, there was a significant negative correlation (P<0.05) between serum aldosterone level, fractional shortening percentage and ejection fraction percentage. There was a negative significant correlation (P<0.001) between serum aldosterone level and E/A ratio (Table IV).

In the uncontrolled hypertensive patients (group B), there was a non significant correlation (P>0.05) between serum aldosterone level and age and sex. There was a significant positive correlation (P<0.05) between aldosterone level, duration of hypertension, mean systolic blood pressure, mean diastolic blood pressure, serum plasma rennin activity, septal wall thickness and posterior wall thickness. There was a significant negative correlation (P<0.05) between serum aldosterone level and fractional shortening percentage. There was a highly significant negative correlation between aldosterone level and ejection fraction percentage and E/A ratio (Table V).

Discussion

In this study we have demonstrated that serum aldosterone levels were elevated in pressure overload. This would be consistent with the hypothesis that aldosterone plays a key role in

Table I. The clinical and biochemical characteristics for all subjects participated in the study (mean ± SD)

Parameters	Group (A)	Group (B)	Group (C)
Age [years]	52.1±8.3	49.6±9.8	56.2±8.9
Sex			
• males	16	18	10
• females	14	12	10
Duration of H.T.N. [years]	12.3±2.3	12.4±1.2	–
M.S.B.P. [mm Hg]	121.2±5.3	168.6±9.7	123.5±6.3
M.D.B.P. [mm Hg]	77.1±4.2	115.3±3.8	78.6±5.2
Serum aldosterone [ng/dl]	10.1±3.2	11.6±5.9	3.8±1.2
Serum plasma renin activity [ng Al/ml]	1.6±0.3	1.9±0.1	0.9±0.2

Group (A) – well controlled hypertensive patients, group (B) – uncontrolled hypertensive patients, group (C) – non-hypertensive patients, M.S.B.P. – mean value of systolic blood pressure, M.D.B.P. – mean value of diastolic blood pressure

Table II. Echo findings of group (A) (well controlled hypertensive patients)

Parameters	PW	Sept.	FS%	EF%	E/A
Mean	1.06	5.6	30.9	58.58	0.88
Standart deviation	0.12	20.57	5.14	6.54	0.18
Variance	0.01	42.31	26.39	42.81	0.03
T test with normal	0.004	0.16	0.003	0.002	4.03
P	<0.05	>0.05	<0.05	<0.05	<0.001

PW – posterior wall thickness, Sept. – septal thickness, FS% – percent of fractional shortening, EF% – percent of ejection fraction

Table III. Echo findings of group (B) (uncontrolled hypertensive patients)

Parameters	PW	Sept.	FS%	EF%	E/A
Mean	1.19	1.24	26.59	51.05	0.9
Standart deviation	0.08	0.09	3.37	6.33	0.21
Variance	0.007	0.008	11.35	40.01	0.05
T test with controlled	0.0001	0.18	0.002	0.0003	0.37
P	<0.05	<0.05	<0.05	<0.001	<0.05
T test with normal	2.5	1.09	2.84	2.84	3.28
P	<0.001	<0.05	<0.001	<0.001	<0.001

Table IV. Echo findings of group (C) (non hypertensive control groups)

Parameters	PW	Sept.	FS%	EF%	E/A
Mean	0.95	0.91	35.41	65.21	1.38
Standart deviation	0.13	0.11	4.64	6.92	0.24
Variance	0.02	0.01	21.57	47.93	0.06

Table V. The correlation of serum aldosterone levels to other clinical and biochemical characteristics and echo findings of all subjects participated in the study

Parameters	Group (A)		Group (B)		Group (C)	
	r	P	r	P	r	P
Age	0.25	>0.05	0.28	>0.05	0.23	>0.05
Sex	0.19	>0.05	0.2	>0.05	0.17	>0.05
Duration of H.T.N.	0.49	<0.05	0.58	<0.05	–	–
M.S.B.P.	0.48	<0.05	0.51	<0.05	0.45	<0.05
M.D.B.P.	0.53	<0.05	0.58	<0.05	0.44	<0.05
S.P.R.A.	0.5	<0.05	0.58	<0.05	0.26	>0.05
PW	0.58	<0.05	0.75	<0.001	0.18	>0.05
Sept.	0.31	>0.05	0.62	<0.05	0.22	>0.05
FS%	–0.61	<0.05	–0.76	<0.05	–0.26	>0.05
EF%	–0.52	<0.05	–0.77	<0.001	–0.23	>0.05
E/A	–0.75	<0.05	–0.79	<0.001	–0.17	>0.05

>0.05 – insignificant correlation, <0.05 – significant, <0.001 – significant correlation

mediating adverse myocardial remodeling with pressure overload. Some of the adverse cardiovascular effects that have been described include, cardiac and vascular fibrosis, left ventricular hypertrophy, congestive heart failure, hypertension, endothelial dysfunction, reduced fibrinolysis and cardiac arrhythmias [15].

Aldosterone promotes renal sodium retention, potentiates the actions of angiotensin II, reduces vascular compliance and may promote hypertension through central nervous system mechanisms [16]. Aldosterone has long been known to mediate water and electrolyte balance by acting on mineralocorticoid receptors in the kidney but the recent studies have demonstrated the presence of these receptors in non classical locations, including the brain, blood vessels and the heart [15].

Based on these data, aldosterone receptor blockers should become increasingly relevant in the treatment of essential hypertension [15]. Recent studies advise the addition of low dose spironolactone to the antihypertensive regimen for subjects with resistant hypertension [17]. Spironolactone resulted in a 30% reduction in mortality among patients with severe congestive heart failure [15].

Many studies have shown that spironolactone lowers high blood pressure, improves endothelial dysfunction reduces left ventricular hypertrophy and lowers the incidence of fatal arrhythmias [15].

However spironolactone, because of its interaction with steroid receptors, is not without side-effects, which include gynecomastia, breast tenderness, menstrual irregularities and male impotence [18].

As a result, eplerenon (INSPRA), a selective aldosterone blocker, is currently being investigated for its efficacy and side effects profile when compared to spironolactone [18].

It has recently been reported that the selective aldosterone antagonist, eplerenon, is a more effective antihypertensive agent than the angiotensin Π receptor blockers, in patients with mild to moderate hypertension [18].

The study revealed an elevation of the serum aldosterone levels in hypertensive patients which was more marked in the uncontrolled cases compared to the normotensive control group. The study also demonstrated a significant correlation between the serum levels of aldosterone and the duration of hypertension, mean systolic blood pressure and mean diastolic blood pressure in both controlled and uncontrolled cases of hypertension.

These findings are in accordance with El Gharbawy el al., 2001 [19], who concluded that the hypertensive black Americans had an elevation of the serum level of aldosterone when compared to white patients with essential hypertension. Vason et al., 2004 [20] reported that the serum aldosterone level was directly related to blood pressure in both sexes and Grim et al., 2005 [21], who found that serum aldosterone levels were correlated with the blood pressure, more consistently and to a greater extent in the black subjects.

Brilla and Maisch 1994 [22] stated that pressure overload of the heart and the growth of the myocardium is the result of enlargement of cardiac myocytes as an adaptation geometry caused by ventricular loading.

Non-myocyte cell growth, including cardiac fibroblast activation, may also occur and cardiac fibroblast activation is responsible for accumulation of type I and II collagen, the major fibrous component of the myocardial collagen matrix, while vascular smooth muscle cell growth accounts for the medial thickening and increased resistance in coronary vessels. This structural remodeling of the cardiac interstitium represents a major determinant of pathological hypertrophy and it accounts for increased myocardial stiffness and cardiac resistance. This leads to ventricular systolic and diastolic dysfunction and ultimately the appearance of symptomatic heart failure.

The pathogenesis of perivascular and interstitial fibrosis involves the response to two types of stimuli, a hormonal one mainly involving the rennin-angiotensin-aldosterone system [23], and a haemodynamic stimulus, particularly high blood pressure. Hypertension is invariably associated with inflammatory call infiltration, either in the intimal part of large vessels or is the adventitial region of arterioles.

El Gharabawy et al., 2001 [19] concluded that left ventricular size and geometry were correlated with serum aldosterone in the obese black Americans, but not in obese French Canadians. In patients with hypertensive heart disease, myocyte hypertrophy and myocardial vessel changes are present but myocardial vascular hypertrophy, not myocyte hypertrophy, determines myocardial stiffness [24].

Angiotensin converting enzyme inhibitors (ACE) appear to delay myocardial fibrosis associated with enhanced collagen degradation, irrespective of left ventricular hypertrophy regression [24]. Aldosterone may induce left ventricular hypertrophy in humans as well as in experimental animals. Also, angiotensin II and aldosterone may differentially participate in causing hypertrophy in humans as well as in experimental animals. Finally, angiotensin II and aldosterone may differentially participate in causing hypertensive target organ damage [25].

Further investigations are warranted to confirm the results of our study and enforce our advice that aldosterone antagonists should be considered as one of the first line treatments of essential hypertension to protect myocardial function in hypertensive patients.

In conclusion, serum aldosterone level increases in pressure overload and aldosterone plays a role in mediating adverse myocardial remodeling in hypertensive patients. Aldosterone receptors blockers may have an important role in controlling hypertension and its complications on the heart. Selective aldosterone antagonists with fewer side effects than spironolactone must be subjected to more studies so that hypertensive patients can benefit from their myocardial protective effects.

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