Original Paper

Arterial Plasma Vasopressin and Aldosterone Predict Left Ventricular Mass in Men Who Develop Hypertension Over 20 Years

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Left ventricular (LV) hypertrophy is related to blood pressure level and neurohormonal factors. The authors previously demonstrated that arterial norepinephrine levels predict LV mass in middle-aged men who developed hypertension through 20 years. The aim of this 20-year prospective study was to investigate arterial vasopressin, aldosterone, and renin as long-term predictors of LV mass. Normotensives (n=17), subjects who developed hypertension (n=17), and sustained hypertensives (n=22) were compared at baseline (42 years) and at follow-up (62 years). There were no significant differences in baseline vasopressin, aldosterone, or renin levels. The group with sustained hypertension had more LV hypertrophy (P=.025) at follow-up. Among new hypertensives, multiple regression analysis demonstrated that baseline arterial vasopressin (β=0.53; P=*.041) and aldosterone (β=0.56;* P=*.032) independently explained LV mass index (*R^2*=0.85;* P=*.035). In conclusion, baseline arterial vasopressin and aldosterone, but not renin, appear to predict LV mass in middle-aged men who developed hypertension over a 20-year period. (J Clin Hypertens. 2007;9:365–371)* ©2007 Le Jacq

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Left ventricular hypertrophy (LVH) is associated with hypertension,[1] predicts cardiovascular complications,[2] morbidity and mortality,[3] and is associated with left ventricular (LV) dysfunction and cardiac arrhythmias.[4] The degree of LVH is partly related to blood pressure (BP) level and partly to neurohormonal factors.[5] Several studies have shown the association between LV mass and the sympathetic nervous system.[6,7] We have previously demonstrated that arterial plasma norepinephrine levels predict LV mass in middle-aged men who developed hypertension over a 20-year period.[8] Experimental studies have shown that vasopressin induces vasoconstriction and myocardial hypertrophy.[9] Development of LVH may also be influenced by the renin-angiotensin-aldosterone system.[5] To our knowledge, however, there are no data available to compare arterial plasma vasopressin, aldosterone, and renin with LV mass over a long-term follow-up in normotensive and hypertensive subjects. The aim of this present prospective study was to investigate the association between baseline arterial plasma vasopressin, aldosterone, and renin levels and LV markers at follow-up after 20 years in groups of sustained normotensives (NT), subjects who developed hypertension through follow-up (new hypertensives [new HT]), and people with sustained hypertension (HT).

METHODS

This cross-sectional study was started in 1984 when subjects were 40 years of age. Because of the relative young age at baseline, follow-up was

performed at the age of 60 years. The age range (40–59 years) was examined in a parallel and larger study.[10] The present study was invasive, with plasma vasopressin, aldosterone, and renin obtained intra-arterially. The cohort consisted of middle-aged Caucasian men of the same sex, age, and race. In 2004, subjects were divided into 3 prespecified groups: NT, new HT, and HT (ie, groups of subjects with clear differences in BP level and development and duration of hypertension).[8]

Study Protocol in 1984

The study protocol in 1984 has previously been described.[11] All the subjects were studied at the same time of day in a quiet room and at a constant room temperature. The subjects fasted and abstained from smoking for the preceding 8 hours and abstained from alcohol for the preceding 24 hours before the studies. Catheters (Venflon; Viggo AB, Helsingborg, Sweden) were introduced under local anesthesia in the left brachial artery. The institutional ethics committee approved the study. All subjects were given oral and written information and provided oral consent for participation.

Subjects in 1984

The hypertensive group consisted of 35 men who had untreated and uncomplicated essential hypertension. Two years earlier, systolic BPs (SBPs) between 140 mm Hg and 170 mm Hg and diastolic BPs (DBPs) between 90 mm Hg and 100 mm Hg were recorded at a health screening. They were included in the 1984 study if they had DBPs between 94 mm Hg and 105 mm Hg on 2 separate occasions. Forty-four healthy men were recruited from the same health screening; they all had BP measurements <140/90 mm Hg. All subjects had normal electrocardiographic (ECG) results, ocular fundi, urinalysis, and kidney function estimated by creatinine clearance. They were all untreated, both before and at the baseline examination.

Biochemical Assays in 1984

Arterial plasma vasopressin (coefficient of variation [CV], 14%) and aldosterone (CV, 5%) were measured by radioimmunoassay techniques and norepinephrine (CV, 9%) by a radioenzymatic method, all described previously.[11–13] The method of plasma renin concentration (CV, 5%) has been described previously.[14]

Study Protocol in 2004

Examination was identical to that of 20 years ago except that arterial catheters were not inserted and ambulatory BP measurement was included at follow-up as this technique was now available. They were examined by the same 2 physicians who were unaware of the participants' BP status. The protocol included the diagnosis *new hypertension,* and assessment was done prospectively before further analysis of data. The Regional Committee for Medical Research Ethics approved the protocol for the follow-up; all participants gave written consent.[8]

Subjects at 20-Year Follow-Up in 2004

Fifty-six subjects (22 hypertensives, 34 normotensives) were available for a 20-year follow-up examination. At the time of follow-up, the NT (n=17) had office SBP <140 mm Hg and DBP <90 mm Hg. The group included subjects (n=7) who had slightly elevated office SBP ≥140 mm Hg and/or DBP ≥90 mm Hg on one occasion but normal day and night 24-hour BP (SBP <125 mm Hg and DBP <80 mm Hg). These subjects were judged not to be hypertensive and were kept in the normotensive group.

New HT (n=7) had office BPs ≥140/90 mm Hg and 24-hour BPs ≥125/80 mm Hg or were taking antihypertensive medication. The same criteria were used for the HT (n=22) who were all hypertensive at follow-up.

Antihypertensive Treatment at 20-Year Follow-Up in 2004

Among new HT, 5 of 17 subjects were on antihypertensive medication. Three were on angiotensin receptor blockers, and 1 each on a β-blocker nitrate and calcium channel blocker. In the HT group, 16 of 22 subjects were taking antihypertensive drugs. Ten subjects were treated with monotherapy; 5 with angiotensin receptor blockers, 2 with calcium channel blockers, and 1 each with a β-blocker, angiotensin-converting enzyme inhibitor, or an α-blocker. At follow-up, the average period of treatment was 9.1±5.2 years for the 2 groups. Six subjects were taking combination regimens. In the group of new HT, 1 subject had coronary heart disease (CHD) and 2 subjects had diabetes mellitus. In the group of sustained HT, 3 subjects had CHD and 1 had renal failure. None of the subjects had a history of stroke. In the sustained NT group, no patients had a history of CHD, stroke, diabetes mellitus, or renal failure.

Dropouts

In the original normotensive group at baseline, 34 of 44 subjects participated at 20-year follow-up. Five subjects had died. Among the hypertensives,

Table I. Characteristics of Groups in 1984 (N=56)

Variable	Normotensives (n=17)	New Hypertensives (n=17)	Hypertensives (n=22)	ANOVA *P*
BMI, kg/m^2	24.0±2.1	24.4±3.7	24.8±2.4	.343
SBP, mm Hg	119±9	121±8	137±8*	<.001
DBP, mm Hg	69±5	71±6	85±7*	<.001
MAP, mm Hg	85±5	88±6	102±7*	<.001
Heart rate, bpm	57±8	55±4	64±13†	.026
Arterial vasopressin, ng/L	3.9±2.6	3.9±2.3	2.7±2.3	.467
Arterial aldosterone, µmol/L	192±131	182±137	171±51	.549
Arterial renin, pg/mL	0.3±0.2	0.4±0.22	0.4±0.3	.537

ANOVA indicates analysis of variance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; and MAP, mean arterial pressure. *P<.001 hypertensives vs new hypertensives and controls. †P<.01 hypertensives vs new hypertensives and controls.

22 of 35 participated (13 were not available for follow-up). Two had died. Among nonparticipants (n=23) and subjects who participated (n=56) at follow-up, there were no significant differences regarding baseline body mass index (BMI) (P=.217), SBP (P=.426), DBP (P=.277), arterial vasopressin (P=.251), norepinephrine (P=.933), or aldosterone (P=.255) levels. ECG, ocular fundi, urinalysis, and kidney function estimated by creatinine clearance were normal. Cardiovascular outcomes are unknown among nonparticipants.

Echocardiography in 2004

Echocardiography was performed by an experienced investigator using a GE-Vingmed Vivid 7 echocardiography System (Horten, Norway) with 1.7-MHz probe in second harmonic mode. The echocardiography investigator had no knowledge about participants' BP status. End-diastolic LV dimensions were used to calculate LV mass by an anatomic validated formula.[15] LV internal dimension and interventricular septal and posterior wall thickness were measured in end-diastole and end-systole according to the recommendations of the American Society of Echocardiography.[16] LVH was defined as LV mass index >116 g/m^2.[17] All participants were in sinus rhythm, and measurements up to 3 cycles were averaged. These echocardiographic measurements have an intraclass correlation coefficient between 0.81 and 0.98 in our laboratory.

BP Measurements

After inclusion in the study, all participants had their office BP measured the same way both at baseline and at follow-up. Office BP was measured using a manual mercury sphygmomanometer. Mean values for SBP and DBP were calculated on the basis of 2 BP measurements. Ambulatory BP was recorded with a validated oscillometric device (model 90207; Spacelab, Redmond, WA). BP was measured every 20 minutes during the day, from 7 AM to 10 PM, and every 30 minutes during the night. The average of all measurements is recorded as 24-hour SBP and DBP. Cuffs with bladders of appropriate size were used. The same device was used in all subjects.

Statistics

SPSS 12.1 (SPSS Inc, Chicago, IL) was used for data management and statistical analyses. Results are presented as mean ± SD. Parametric tests were used for normally distributed data. Non-normally distributed data were natural log transformed. Differences between the 2 groups were assessed by Student t test. After subdivision into 3 groups, comparisons were performed by analysis of variance (ANOVA) with linear trend analysis. Univariate relation between variables were assessed by Pearson (r) correlation coefficient and further examined with multiple linear regression analysis using an enter procedure with assessment of colinear diagnostics.

Regression analysis was used to assess whether arterial plasma vasopressin, aldosterone, and renin independently predicts LV mass index and relative wall thickness over 20 years. The regression models used LV mass index as a dependent variable, as this takes height and weight (ie, body surface area) into account. This variable more correctly demonstrates the relationship to LV hypertrophy.[2,17] Hormones, BPs, and body build are all known to impact LV mass measurements,[9,18,19] and heart rate is suggested as a marker of sympathetic activity.[20] These parameters were therefore considered as variables in the regression analysis. Age was not considered as a variable since the participants were all at the same age at examination. A 2-tailed P value <.05 was considered statistically significant.

Table II. Characteristics of Groups in 2004 (N=56)

Variable	Normotensives (n=17)	New Hypertensives (n=17)	Hypertensives (n=22)	ANOVA *P*
BMI, kg/m^2	26.2±2.8	26.9±4.0	28.1±3.8	.121
SBP, mm Hg	135±12	150±11*	165±24†‡	<.001
DBP, mm Hg	86±6	95±8§	102±8†‡	<.001
MAP, mm Hg	102±7	113±8§	123±12†‡	<.001
Heart rate, bpm	65±7	64±9	71±10‖¶	.031
24-h SBP	118±5	130±13§	135±13†	<.001
24-h DBP	72±4	79±8*	85±9†¶	<.001
LV mass index, g/m^2	102±17	111±25	114±20	.071
LV mass, g	200±29	227±62	233±39#	.025

ANOVA indicates analysis of variance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; and LV, left ventricular. *P<.05 new hypertensives vs controls. †P<.001 hypertensives vs controls. ‡P<.01 hypertensives vs new hypertensives. §P<.01 new hypertensives vs controls. ‖P<.01 hypertensives vs controls. ¶P<.05 hypertensives vs new hypertensives. #P<.05 hypertensives vs controls.

Table III. Bivariate Correlates of LV Mass Index and LV Mass in Men Who Developed Hypertension During 20-Year Follow-Up (n=17)

	LV Mass Index		LV Mass	
Variables (1984)	*R*	*P*	*R*	*P*
Systolic blood pressure, mm Hg	0.32	.214	0.41	.103
Diastolic blood pressure, mm Hg	0.39	.119	0.54	.024
Mean arterial pressure, mm Hg	0.41	.102	0.55	.021

LV indicates left ventricular.

RESULTS

At baseline there were, by definition, significant differences in BP between the NT and new HT compared with the HT (P<.001, ANOVA) groups, but there were no significant differences between the NT and new HT groups. At the time of follow-up, there were significant differences among all groups regardless of antihypertensive treatment (P<.001). For LV mass (P=.025) there was a significant trend at follow-up. There tended to be a difference in LV mass index, but this did not reach a level of significance. No significant differences were found between the 3 groups regarding baseline arterial plasma vasopressin, aldosterone, and renin. Further baseline and follow-up characteristics of the 3 groups are given in Table I and Table II.

Univariate Correlations: Baseline Arterial Plasma Vasopressin, Aldosterone, and Renin vs LV Parameters at Follow-Up

Among the new HT subjects, vasopressin correlated positively with LV mass (r=0.52; P=.032) and LV mass index (r=0.34; P=.177). Aldosterone correlated more weakly with LV mass (r=0.28; P=.325) and LV mass index (r=0.20; P=.499). There was no significant association of renin to LV mass (r=0.01; P=.963) and LV mass index (r=0.13; P=.615). In the same group, baseline norepinephrine correlated positively with LV mass (r=53; P=.028) and LV mass index (r=0.50; P=.043), and baseline BMI correlated with both LV mass (r=0.65, P=.005) and LV mass index (r=0.51; P=.039) at follow-up (Figure).

Correlations between baseline BPs and parameters are given in Table III.

Multivariate Regression Analysis: Baseline Arterial Plasma Vasopressin, Aldosterone, and Renin as Predictors of LV Mass Index at Follow-Up

Among new HT subjects, multiple regression analysis was performed with LV mass index at follow-up as a dependent variable. Baseline arterial aldosterone, renin, vasopressin, norepinephrine, BMI, pulse pressure, mean arterial pressure, and heart rate were entered as explanatory variables. In this model, arterial aldosterone (β=0.56; P=.032), vasopressin (β=0.53; P=.041), norepinephrine (β=0.52; P=.032), and BMI (β=0.61; P=.029) were independently associated with variation of LV mass index through 20 years. Pulse pressure demonstrated a borderline association (β=0.57; P=.050). The other covariates, mean arterial pressure, heart rate, and renin, did not reach a level of significance (R^2=0.85; P=.035, whole model).

Altogether, in the regression model baseline, arterial vasopressin and aldosterone independently predicted LV mass index over 20 years in subjects prone to develop hypertension. Such relationships

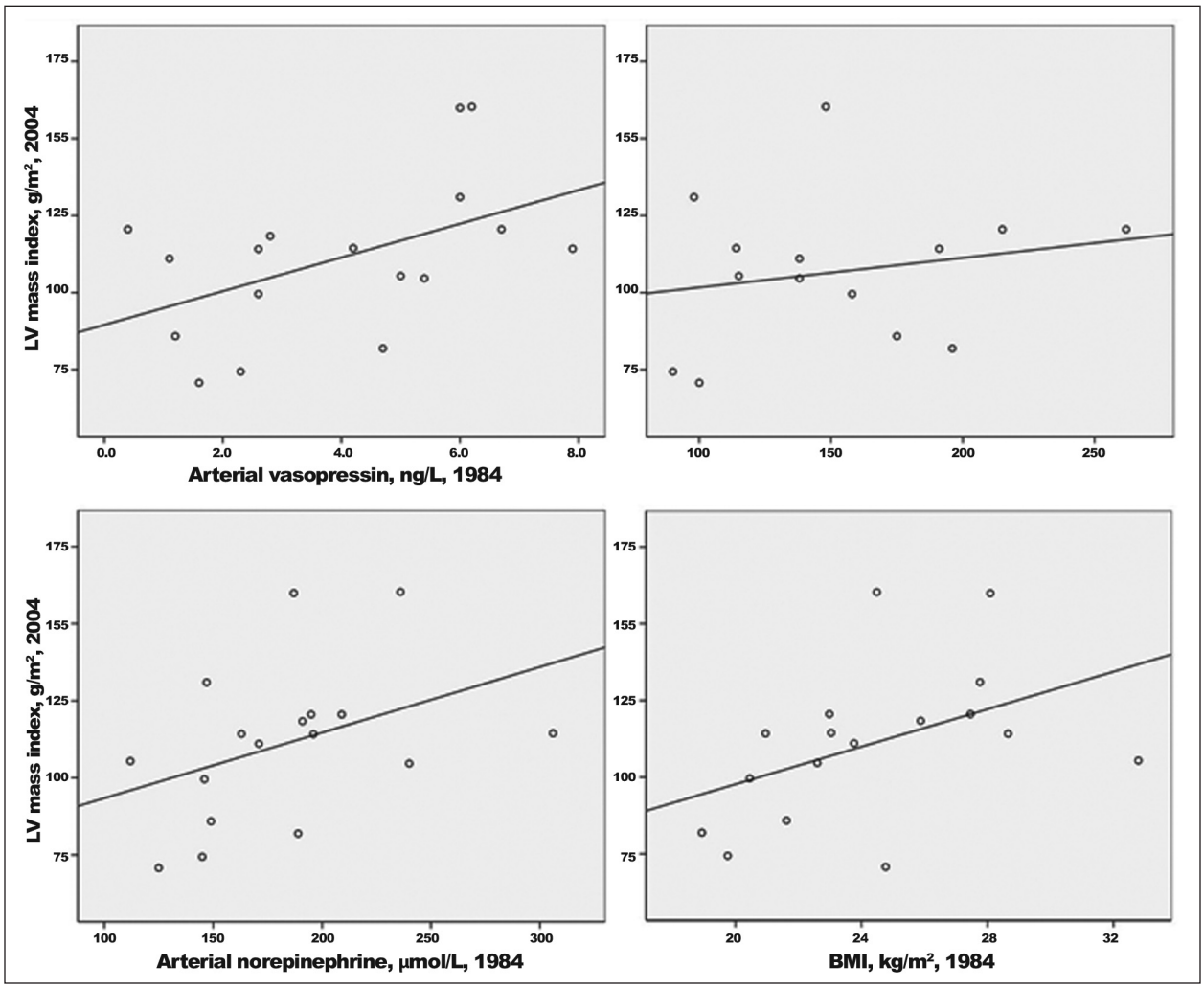

Figure. Correlations between baseline vasopressin, aldosterone, norepinephrine, and body mass index (BMI) vs left ventricular (LV) mass index at follow-up in subjects prone to develop hypertension over 20 years (n=17).

were not found among the NT, or among the HT, of whom 16 of 22 subjects were treated with antihypertensive drugs.

DISCUSSION

In this 20-year prospective study, we investigated the ability of arterial plasma vasopressin, aldosterone, and renin to predict LV parameters in groups of sustained hypertensives, subjects who developed hypertension during follow-up, and sustained normotensives. We found baseline arterial plasma vasopressin and aldosterone to be independent predictors of LV mass index at follow-up among subjects who developed hypertension. In this model, however, plasma renin was not a significant predictor of LV mass.

To our knowledge, it has not been previously demonstrated that arterial plasma vasopressin and aldosterone independently predict LV mass index in people prone to develop hypertension over a long period. While there were no significant differences in hormone levels among the groups at baseline, there was a positive correlation between baseline arterial plasma vasopressin and LV parameters at follow-up among the new HT group. There was no association between arterial aldosterone and LV mass index in univariate correlation. Both arterial plasma vasopressin and aldosterone, however, predicted LV mass index in multivariate analysis. This suggests an influence by vasopressin and aldosterone on LV mass in this group of subjects, an effect that is not seen among normotensives or sustained hypertensives.

Vasopressin activity may be mediated through 3 subtypes of receptors. The V_{1a} receptor subtype is found in the myocardium and vascular smooth muscle cell, among others.[9] It has been shown that a possible mechanism for developing LVH could be due to changes in activity at the post-receptor level; this is induced by vasopressin binding to

the V_{1a} receptor subtype in the cardiomyocytes. This activation leads to increased myocardial cell hypertrophy by enhancing protein synthesis and cellular growth. There is evidence that protein kinase C, an intracellular mediator of hypertrophic growth, is activated during the process induced by vasopressin.[21] These changes at the post-receptor level in the myocardium could explain that, despite the lack of difference in levels of arterial vasopressin among the NT and new HT at baseline, these levels predict LV mass changes in people prone to develop mild hypertension. A direct effect of vasopressin at the V_1 receptor of fibroblasts has also been proposed as a pathophysiologic process for LVH by promoting cardiac fibroblast proliferation.[22] Aldosterone is known to mediate tissue injury through a variety of mechanisms and plays a role in the development of myocardial hypertrophy and fibrosis.[23] It may potentiate sympathetic activity by inhibition of norepinephrine uptake and may also stimulate the up-regulation of angiotensin type 1-receptors. Furthermore, aldosterone affects endothelial function and vascular smooth muscle cell hypertrophy.[24]

As previously discussed,[8] the present study utilized arterial samples. This limited sample size was a result of the invasive nature of the study and the long period of follow-up. Prior to this study, we had been especially concerned about arterial cathecolamines.[25] Since the catecholamines were sampled in arterial blood, the other hormones were also measured by arterial samples.

This study was preplanned; however, it can be considered a pilot study because of the limited number of participants. The homogeneity of the participants and standardized protocol to a certain degree compensate for the limited sample size (ie, they were all Caucasian men of the same age). All participants had normal ECG results, ocular fundi, urinalysis, and kidney function estimated by creatinine clearance. All participants were examined over a limited period. We studied subjects known to develop hypertension; findings might not be extrapolated to healthy normotensives, as they could have other mechanisms affecting LV mass. We did not find any predictive factors among the sustained hypertensives, but many were treated with antihypertensive medication, which might have biased the results. Bias of the hormonal analysis might have interfered with the results, but confidence intervals of the different biochemical techniques are acceptable and were all done by the same technician.

In previous studies, hypertensive subjects have been found to have significantly higher vasopressin[26] and aldosterone[27] levels than normotensives, but the hypertensives in our study had only mildly elevated BP at baseline. We can only speculate about whether a population with more pronounced and untreated hypertension would have a more significant correlation between baseline arterial plasma vasopressin and aldosterone and LV mass at follow-up.

In 1984, echocardiography was not available to exclude LVH. Our first echocardiographic investigation of hypertensives was in 1986.[7] It seems unlikely, however, that LVH was present in 1984 and particularly not in those who were characterized as normotensives and otherwise healthy. No participants had signs of LVH on baseline ECG or chest x-ray. These findings cannot entirely exclude presence of LVH. It is uncertain whether a change in LV mass could have been detected and, therefore, given more information that could be taken into account based on the inaccuracy of the echocardiographic technique in 1984.

In this 20-year follow-up study, it appears as if arterial vasopressin and aldosterone, but not renin, levels are potent factors that influence LV mass in subjects prone to develop hypertension, ie, these hormone levels suggest significant influence on LV mass over time. This might be the result of a direct effect at the receptor level and enhanced post-receptor activity in the myocardium in the LV, and not necessarily because of high circulating hormone levels.

CONCLUSIONS

This prospective pilot study suggests that baseline arterial vasopressin and aldosterone, but not renin, predict LV mass in middle-aged men who developed hypertension through a 20-year follow-up. These data support a relationship between vasoactive neurohormone activity and LV mass in subjects with essential hypertension.

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