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Original Article

Relationship between circulating concentration of Ang II, ADM and ADT and left ventricular hypertrophy in hypertension

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Abstract: Background: Left ventricular hypertrophy (LVH) is the most common structural damage in hypertensive complication and is an independent risk factor for assessing cardiovascular events. The aim of this study was explore the relationship between plasma concentration of angiotensin II (Ang II), Adrenomedulin (ADM) and adrenotensin (ADT) in patients with hypertension and LVH. Methods: We enrolled 310 hypertensive patients from the department of cardiology of Tianjin Union Medical Center as the hypertension group and 39 healthy subjects as control group. Further grouping according to the LVMI (male LVMI≥115 g/m^2, female LVMI≥95 g/m^2) values for determining LVH in the 2013 ESC Hypertension Management Guidelines. Plasma levels of Ang II, ADM and ADT were measured using ELISA assay. Results: The levels of plasma Ang II and ADM in essential hypertension (EH) were significantly higher than control group, and the essential hypertension combined left ventricular hypertrophy (EHCLVH) group was higher than essential hypertension not with left ventricular hypertrophy (EHNLVH) group (P<0.05). Correlation analyze showed that left ventricular mass index (LVMI) was positively related to Ang II and ADM, and negatively related to ADT. Logistic regression analyze indicated that LVH are strongly linked with systolic blood pressure (SBP), Ang II, ADM and ADT. ROC curve showed ADM and ADT have similar value in distinguish LVH. Conclusion: Plasma levels of Ang II, ADM and ADT might act as indicator to identify hypertensive LVH.

Keywords: Hypertension, left ventricular hypertrophy, angiotensin II, adrenomedulin, adrenotensin

Introduction

Left ventricular hypertrophy (LVH) is the most common structural damage in hypertensive target organ damage and an independent risk factor for assessing cardiovascular events, such as sudden cardiac death, coronary heart disease, myocardial infraction, heart failure and stoke [1, 2]. Study has shown that patients with LVH have a 65% increase in cardiovascular events and a 49% increase in all-cause mortality compared with non-LVH patients [3]. It has been found that in some hypertensive patients with long-term blood pressure (BP) control, the left ventricular mass continues to increase, indicating that stress and volume load are not the only factors leading to hypertensive LVH [4, 5].

Neurohumoral factor are involved in the development of LVH in hypertension, in which circulating and local angiotensin II (Ang II) play an important role in vasoconstriction, myocardial hypertrophy and fibrosis [6]. Several animal experiments proved that Ang II had receptor mediated effects on inducing cardiac hypertrophy and increase of left ventricular mass (LVM) [7, 8]. In clinical trial, Ang II receptor blocker significantly reduces ventricular mass, improves LV structure parameters in patients with hypertension [9].

Adrenomedulin (ADM) is an active peptide with vasodilating action extracted in human pheochromocytoma in 1993. Research confirmed that pro-adrenomedulin (pro-ADM) is composed of 185 amino acid residues and is hydrolyzed by endogenous N-peptide to form four enzymatic products, namely pro-ADM$_{22\text{-}42}$ (PAMP), pro-ADM$_{45\text{-}92}$, pro-ADM$_{95\text{-}146}$, (ADM) and pro-ADM$_{153\text{-}185}$ (ADT). Among them, ADM has the functions of dilating blood vessels, lowering BP,

inhibiting the migration and proliferation of vascular smooth muscle cells [10], and ADT has antagonistic and mutual inhibition effects with ADM. Intravenous injection of exogenous ADM in hypertensive rats significantly increased the concentration of cAMP, accompanied by decreased blood pressure and delayed cardiac hypertrophy, suggesting that ADM is involved in the pathogenesis of hypertension and LVH [11].

At present, the role of ADM, ADT and Ang II in the pathogenesis of hypertensive left ventricular hypertrophy and the relationship between them are rarely reported. Hence, we measure the plasma levels of Ang II, ADM and ADT in subjects to explore their relationship in essential hypertension (EH) and EH combined LVH, and provide evidence for prevention and treatment of target organ in hypertension.

Patients and methods

Study population

From December 2016 to October 2017, 310 inpatients with essential hypertension admitted to Tianjin Union Medical Center were enrolled, including 180 males and 130 females. Thirty nine elderly healthy volunteers who underwent physical examination at the same time in our hospital were admitted as control group. The diagnosis and classification of hypertension conforms the 2013 European Society of Cardiology (ESC) practice guidelines [12], that is, the BP is measured by SBP≥140 mmHg and/or DBP≥90 mmHg. Hypertension combined with LVH diagnostic criteria based on 2013 ESC Guidelines for Hypertension Management, Diagnostic Criteria for left ventricular mass index (LVMI)≥115 g/L (male), LVMI≥95 g/L (female). Patients excluded from the following conditions: secondary hypertension, diabetes, heart failure, chronic renal disease, severe liver disease, peripheral vascular disease, anemia, malignant tumor, valvular heart disease, hypertrophic cardiomyopathy, congenital heart disease and immune system diseases. Informed consent was obtained from all subjects, and the study was approved by the Ethics Committee board of Tianjin Union Medical Center.

Study procedures

Baseline characteristics were obtained to establish a database. In the hypertension group, the highest systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) values measured in the past 3 days were registered, and the control group registered the average of 3 blood pressures in peace. Fasting venous blood were collected to detect renal function, serum lipid, blood glucose and BNP, Ang II, ADM and ADT. Transthoracic Doppler echocardiography was performed to detect left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT) and E/A value. Devereux formula was performed to obtain LVMI value. LVMI=1.04 [(LVEDD+LVPWT+IVST)^3-LVEDD^3]-13.6; LVMI (g/m^2)=LVM/BSA. According to the LVMI values calculated by the formula, patients with EH were divided into high blood pressure without LVH group and hypertension with LVH group.

Measurement of Ang II, ADM and ADT

Fasting venous blood were obtained on hospital admission and centrifuged to collect plasma. Plasma concentration of Ang II, ADM and ADT levels were measured with the Human enzyme-linked immunosorbent assay (ELISA) according to the instructions of the manufacturer, and the kits were purchased from Qiyi Biological Co. (Shanghai, China). The protocols of this assay have been performed in detail earlier [13]. The other biochemical parameters were measured in the clinical laboratory in Tianjin Union Medical Center. The detection range of Ang II, ADM and ADT were 8 ng/L-150 ng/L, 2 ng/L-40 ng/L and 2 pg/ml-80 pg/ml and the within-run coefficient of variation <9%.

Statistics analysis

Data were analyzed using the statistical package for the social sciences (SPSS Inc., Chicago, IL) version 22.0. Normally distributed, continuous data are expressed as mean values (Mean ± SD). The Discrete variables were expressed as numbers and percentages. The categorical variable is represented percentages. Normality for the continuous variables was performed by the Kolmogorov-Smirnov (K-S) test. Two groups with normal distribution were analyzed by t-test, multiple group comparison using ANOVA analysis. Kruskal-Wallis test for continuous variables of skewed distribution, *P* value is corrected by the formula p'=2α/K(K-1), α=0.05. Pearson lin-

Table 1. Demographic characteristics

	Control (n=39)	Hypertension (n=310)	*P*
Age (years)	65.87±7.23	65.23±12.38	0.752
Male gender (%)	56.4	58.1	0.844
BMI (kg/m^2)	24.06±3.52	25.82±3.41	0.003**
Smoking (%)	69.2	58.4	0.194
Duration (years)	0	6.00 (2.00, 19.00)	0.000**
SBP (mmHg)	119.36±10.92	175.55±20.05	0.000**
DBP (mmHg)	77.49±8.19	98.60±13.76	0.000**
HR (bpm)	66.56±7.09	75.16±12.85	0.000**
TC (mmol/l)	4.59±0.84	5.05±1.84	0.124
TG (mmol/l)	1.12±0.39	1.65±0.82	0.000**
LDL-C (mmol/l)	3.13±0.49	3.29±1.48	0.490
GLU (mmol/L)	5.31±0.53	6.08±2.13	0.067
Cr (umol/L)	69.28±13.04	71.68±18.32	0.491
BNP (pg/ml)	23.90 (17.50, 35.10)	62.96 (30.15, 88.64)	0.000**
eGFR (ml/min/1.73 m^2)	97.10±13.72	82.36±20.64	0.000**
UA (umol/L)	298.69±81.68	320.68±99.54	0.186
E/A<1 (%)	5.10	70.0	0.000**
LVEF (%)	55.02±3.32	55.04±3.61	0.974

Values are mean + SD or median (25th, 75th percentiles). **P<0.01 vs. Control group. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Cr, creatinine; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; UA, uric acid; LVEF, left ventricular ejection fraction.

ear correlation analysis was used for bivariate distribution of normal distribution, spearman correlation analysis was performed for non-conformity analysis. Multiple linear regressions were used to analyze the correlation between multiple parameters. The receiver operator characteristic (ROC) curves were performed to analyze the diagnosis value of Ang II, ADM and ADT levels for hypertension combined LVH. The results are expressed as 95% confidence interval (CI) of the area and area under the curve, P<0.05 (bilateral) was statistically significant.

Results

Demographic characteristics

Our object of study was comprised of 310 patients with EH, 39 healthy controls. The baseline characteristics were shown in **Table 1**. Compared with control group, the BMI, SBP, DBP, heart rate (HR), triglyceride (TG), brain natriuretic peptide (BNP) and E/A ratio were significantly increased in EH group (P<0.05), and estimated glomerular filtration rate (eGFR) was significantly decreased in EH group (P<0.05).

Comparison of Biomarker concentration and related parameters with LVH

As shown in **Figure 1**, the concentration of LVMI, ADM and ADM were significantly raised in hypertension group, ADT level was shown opposite trend (P<0.01). Spearman correlation analysis shows that Ang II, ADM and ADT were closely related with duration of hypertension, BP, LVMI, and ultrasound index of ventricular hypertrophy (E/A ratio, LA, LVEDD, LVST and LVPWT) (Supplementary Table 1). In addition, according to the LVMI values (male ≥115, female ≥95) of 2013 ESC management guidelines, patients with hypertension were divided into essential hypertension non-left ventricular hypertrophy (EHNLVH) and essential hypertension combined left ventricular hypertrophy (EHCLVH). As shown in **Table 2**, except for age and LVEF, the duration of hypertension, SBP, left atrium (LA), left ventricular end-diastolic pressure (LVEDD), left ventricular posterior wall thickness (LVPWT), interventricular septum thickness (LVST), Ang II, ADM and ADT were significantly different between three groups (P<0.01). These results indicate that LVH is closely associated with long-term hypertensive state, circulating Ang II, ADM stimulation and ADT reduction, and ultimately leading to ventricular remodeling.

Relationship between Ang II, ADM and ADT and LVH in hypertension patients

For further understand the relationship of Ang II, ADM and ADT with left ventricular hypertrophy, Spearman correlation was performed and the results indicated that Ang II (r=0.52, P<0.01) and ADM (r=0.548, P<0.01) were positively correlated with LVMI, the key indicator for judging LVH (P<0.01). However, ADT (r=-0.634,

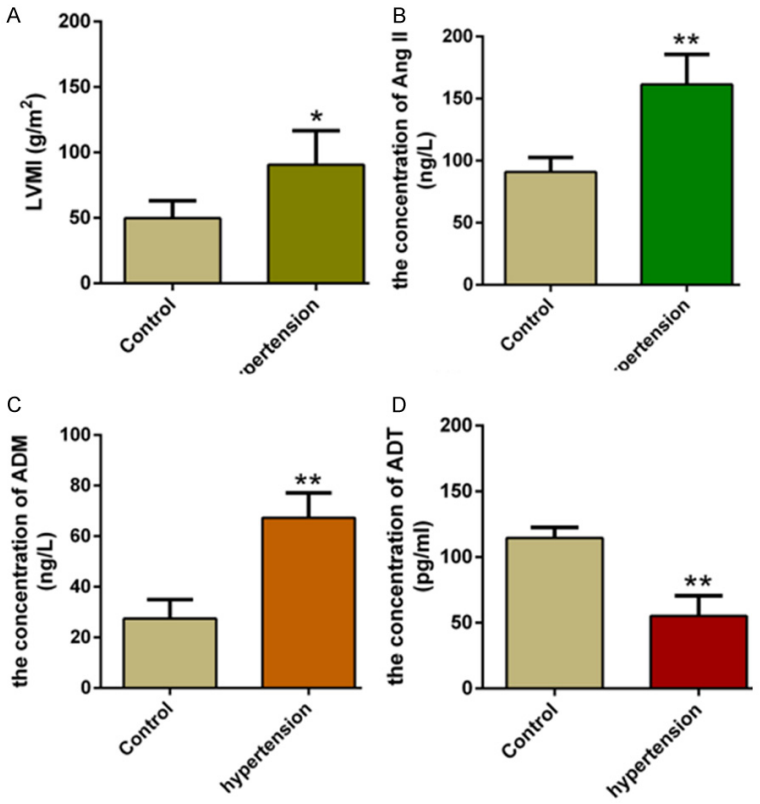

Figure 1. The value of LVMI and plasma levels of Ang II, ADM and ADT. **P*<0.05 ***P*<0.01 vs. Control group.

P<0.01) was negatively correlated with LVMI, which suggests that ADT have antagonistic effects with ADM and Ang II in the process of LVH (**Figure 2**). In addition, hypertension patients with or without LVH as the dependent variable, age, hypertension duration, BMI, SBP, DBP, blood glucose, TC, TG, LDL-C, Ang II, ADM and ADT as independent variables to establish multiple independent logistic regression model, the equation is Ln (odds)=β0+β1X1+...+βpXp. As shown in **Table 3**, the ktrans was 3.932, and the regression coefficient of SBP, Ang II, ADM and ADT were 0.117, 0.155, 0.178 and -0.16 (*P*<0.05), respectively. Hence, the Logistic regression equation is: Y (EHNLVH or EHCLVH)=3.932+0.117 (SBP)+0.155 (Ang II)+0.178 (ADM)-0.160 (ADT). These results indicate that Ang II, ADM and ADT are involved in the pathological change of EHCLVH.

Diagnostic value of Ang II, ADM and ADT in hypertension patients with LVH

As show in **Figure 3**, LVST and LVPWT showed the highest area under the ROC curve (AUC) to detect LVH with an AUC of 0.951 (95% CI: 0.930, 0.972) followed by Ang II with an AUC of 0.938 (95% CI: 0.910, 0.966). The AUC for LA (AUC: 0.885, 95% CI: 0.849, 0.922) and ADT (AUC: 0.838, 95% CI: 0.792, 0.885) was superior to duration of hypertension in prediction of LVH. For ADM the AUC was 0.739 (95% CI: 0.679, 0.798). The cut-off values of Ang II, ADM and ADT for diagnosing LVH were 160.81 ng/L, 53.494 ng/L and 50.556 pg/ml, respectively (**Table 4**). These results indicated that Ang II, ADM and ADT have similar diagnostic value of cardiac ultrasound parameters (LVST, LVPWT).

Discussion

In this study, we compared circulating concentration of biomarkers that regulating vasomotor function-Ang II, ADM and ADT in essential hypertension patients and control from same hospital. We found that circulating Ang II and ADM were significantly increased in patients with hypertension, and ADT was significantly decreased. This trend is also remarkable in the EHCLVH group compared to the EHNLVH. Correlation analysis showed that Ang II, ADM and ADT were closely related with hypertensive LVH. Further results indicated that measurement of Ang II, ADM and ADT in the circulation provide additional predictive value similar to LVMI for identifying early heart damage in hypertensive.

Elevated blood pressure activates the Renin-angiotensin-aldosterone System (RAAS) system to promote the secretion of Ang II in plasma, resulting in strong contraction of small arteries and increased synthesis and secretion of aldosterone (ALD), which in turn affects the content of ventricular BNP and type III procollagen amino acid ends (PIIINP) and triggers the configuration change of heart [14, 15]. Study have shown that locally secretion of Ang II in heart is higher in hypertensive patients, the growth factor-like effects of Ang II promotes

Table 2. Association of Biomarker levels and clinical parameters with left ventricular hypertrophy

	Control (n=39)	EHNLVH (n=177)	EHCLVH (n=133)	*p*-value
Age (years)	65.87±7.23	64.78±12.69	65.84±11.96	0.707
Duration (years)	0	5.00 (2.00, 10.00)[a]	10.00 (4.25,20.00)[a,b]	0.000**
SBP (mmHg)	119.36±10.92	168.95±17.19[a]	184.35±20.28[a,b]	0.000**
DBP (mmHg)	77.49±8.19	98.68±11.61[a]	98.49±16.23[a]	0.000**
LA (mm)	24.26±3.26	27.39±5.39[a]	35.56±3.925[a,b]	0.000**
LVEDD (mm)	39.55±2.78	45.22±3.18[a]	47.85±3.86[a,b]	0.000**
LVPWT (mm)	7.49±1.12	8.56±0.91[a]	10.76±0.93[a,b]	0.000**
IVST (mm)	7.49±1.12	8.56±0.91[a]	10.76±0.93[a,b]	0.000**
LVMI (g/m^2)	49.67±13.43	71.05±13.59[a]	112.03±16.33[a,b]	0.000**
LVEF (%)	55.02±3.32	55.36±3.51	54.61±3.69	0.192
E/A<1 (%)	5.1%	62.70%[a]	79.70%[a,b]	0.000**
Ang II (ng/L)	90.98±11.60	125.69±30.39[a]	209.03±40.49[a,b]	0.000**
ADM (ng/L)	27.47±7.74	46.93±7.25[a]	62.02±19.13[a,b]	0.000**
ADT (pg/mL)	114.57±8.03	62.82±12.57[a]	45.16±12.53[a,b]	0.000**

Values are mean + SD or median (25th, 75th percentiles). [a]P<0.05 vs. Control group; [a,b]P<0.05 vs. EHNLVH group. **P<0.01 means a difference between the groups. SBP, systolic blood pressure; DBP, diastolic blood pressure; LA, left atrium; LVEDD, left ventricular end-diastolic pressure; IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; Ang II, angiotension II; ADM, adrenomedulin; ADT, adrenotensin.

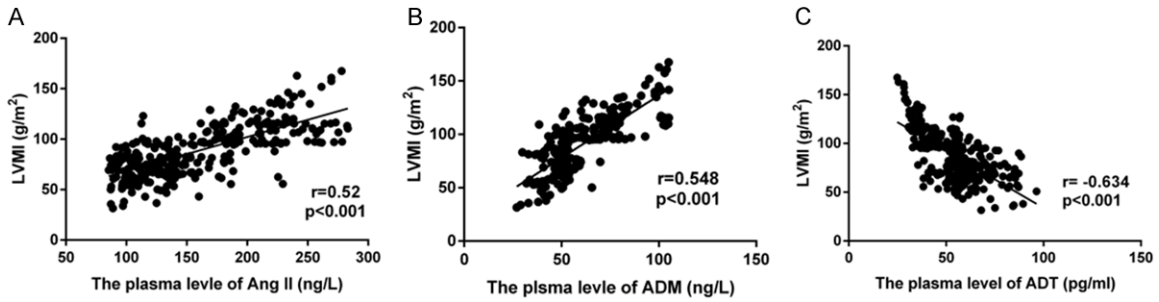

Figure 2. Correlation analysis of LVMI with Ang II, ADM and ADT. P<0.05 indicates statistically significant.

proliferation of fibroblast and myocardin, changes the proportion of type I collagen and type III collagen, eventually causing cardiac stiffness [16, 17]. Our results shown that rather strong associations of Ang II with several echocardiographic parameters, especially IVST and LVPWT, strengthening the usefulness of circulating Ang II as an indicator of hypertensive LVH. It is worth noting that the size of LA and E/A ratio in the hypertension group were obviously higher than in the control, and there is a significant positive correlation between Ang II and LA and E/A ratio, indicating that the increase of Ang II might be a marker indicative to some extent of diastolic function [18].

ADM exerts counter-regulatory effects on Ang II-induced actions, since ADM potently inhibited Ang II-induced collagen deposition surrounding the coronary arteries and myofibroblast differentiation and expressions of extracellular matrix-related genes in rats [19]. Therefore, ADM is considered as a biomarker for heart failure due to its inhibition of cardiomyocyte hypertrophy, fibroblast proliferation and collagen deposition [20]. Inhalation or intravenously administered of ADM significantly reduced pulmonary arterial pressure and reverse pulmonary artery remodeling [21]. The mechanism of ADM dilated blood vessels and decreased blood pressure mainly includes enhancing nitric oxide synthase activity to promote oxide synthase (NO) secretion, inhibiting endothelin release and binding to receptors and vasodilation via cAMP [22, 23]. It is more important that the inhibition of endogenous ADM secreted from the cardiomyocytes with the anti-ADM monoclonal antibody increased protein synthe-

Table 3. Logistic regression analysis of two-class dependent variables affecting LVH in patients with hypertension

	B	*P*	Exp (B)	EXP (B) 95% CI	
				Upper	Lower
Age (years)	-0.016	0.486	0.985	0.943	1.029
Duration (years)	0.029	0.239	1.030	0.981	1.081
BMI (kg/m^2)	0.110	0.104	0.895	0.784	1.023
SBP (mmHg)	0.117	0.021*	1.018	1.001	1.046
DBP (mmHg)	-0.028	0.125	0.973	0.938	1.008
GLU (mmol/L)	0.272	0.089	1.312	1.028	1.675
TC (mmol/L)	-0.059	0.792	0.943	0.608	1.461
TG (mmol/L)	0.269	0.376	1.309	0.721	2.376
LDL-C (mmol/L)	-0.217	0.476	0.805	0.443	1.463
Ang II (ng/L)	0.155	0.000**	1.056	1.042	1.071
ADM (ng/L)	0.178	0.008**	1.081	1.021	1.145
ADT (pg/mL)	-0.160	0.005**	0.942	0.903	0.982
Ktrans	3.932	0.323	0.020		

*P<0.05, **P<0.01 means statistically significant. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Ang II, angiotension II; ADM, adrenomedulin; ADT, adrenotensin.

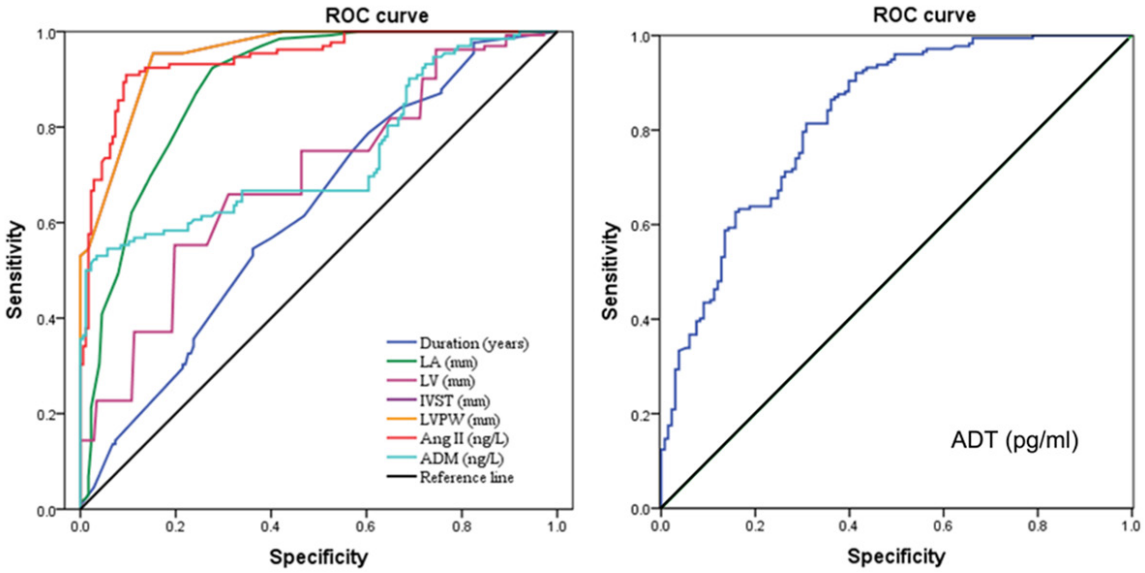

Figure 3. ROC curve for diagnosis hypertensive LVH.

sis, indicating that endogenous ADM play a possible autocrine or paracrine role to inhibit cardiomyocyte hypertrophy [24]. Above results appears that the anti-hypertrophic action of AM may not be explained by cAMP signaling alone.

Both ADM and ADT are act as circulating hormones and local paracrine mediators with multiple biological activities, which are involved in the regulation of cardiovascular system homeostasis [25, 26], but they have the opposite regulation of vasoactive activity. Isolated aorta exhibits contractile properties in K-H solution containing ADT [23]. Increasing concentration of Ang II and AT1 receptors after ADT treatment mediate the stimulatory effects of ADT on cell proliferation, extracellular matrix synthesis and secretion [27]. Our data show that the plasma concentrations of ADM and ADT have inverse trends, and regression analysis suggests that

Table 4. Diagnostic value of factors affecting left ventricular hypertrophy

	AUC	95% CI	*P*	Cut-off value
Duration (years)	0.691	(0.557, 0.681)	0.000**	-
LA (mm)	0.885	(0.849, 0.922)	0.000**	-
LVEDD (mm)	0.692	(0.632, 0.751)	0.000**	-
IVST (mm)	0.951	(0.930, 0.972)	0.000**	-
LVPWT (mm)	0.951	(0.930, 0.972)	0.000**	-
Ang II (ng/L)	0.938	(0.910, 0.966)	0.000**	160.810
ADM (ng/L)	0.739	(0.679, 0.798)	0.000**	53.494
ADT (pg/L)	0.838	(0.792, 0.885)	0.000**	50.556

**$P<0.01$ were considered statistically significant.

both of ADM and ADT are independent risk factors for EHCLVH. Considering the compensatory response during the formation of elevated BP and myocardial remodeling caused by mutual antagonism between synthesis and release. The mechanism by which ADT causes LVH is unclear. We speculate that it may be related to the intramolecular regulation of pro-ADM, and may also be related to ADT promoting the synthesis and secretion of Ang II, AT1 expression or activation of cAMP pathway [28, 29].

Ang II is the most important effector in the RAAS system, so the detection of Ang II is important for judging the activity of the RAAS system and understanding the heart damage. However, the plasma concentration of Ang II is easy effected by posture body, so it has certain limitations in clinical application. Our correlation analysis result showed Ang II was positively related to ADM and negatively related to ADT. The results of ROC curve indicated that Ang II, ADM and ADT have similar diagnostic value for hypertensive ventricular hypertrophy, suggesting that the detection of ADM and ADT levels in patients with hypertension can replace Ang II as an indicator of RAAS system activity and hypertensive ventricular hypertrophy, and guide the clinical treatment of hypertensive heart damage.

This study has some potential limitations. The overall sample size was small since limited by our research center. Besides, The mechanism for the development of EH and cardiac damage in Ang II, ADM, and ADT requires further validation by animal experiments.

In conclusion, our study found that patients with EHCLVH had significantly higher plasma levels of Ang II and ADM and lower ADT level than patients with EHNLVH, suggesting that all three might involve in pathogenesis of LVH. Moreover, a satisfactory correlation between Ang II, ADM and ADT was observed in patients with hypertension. ADM and ADT can be used as indicators to reflect the activation of RAAS system, and provide guidance for the diagnosis and treatment of early heart damage in EH.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Correlation analysis between Ang II, ADM, ADT and related parameters of hypertension

	Ang II		ADM		ADT	
	r	*p*	r	*p*	r	*p*
Age (years)	0.034	0.521	-0.036	0.497	-0.015	0.785
Duration (years)	0.304	0.000**	0.221	0.000**	-0.299	0.000**
SBP (mmHg)	0.517	0.000**	0.491	0.000**	-0.656	0.000**
DBP (mmHg)	0.185	0.001**	0.231	0.000**	-0.376	0.000**
BNP (pg/ml)	0.347	0.000**	0.313	0.000**	-0.340	0.000**
Cr (μmol/L)	0.039	0.467	0.121	0.023*	-0.070	0.192
eGFR (ml/min/1.73 m^2)	-0.197	0.000**	-0.328	0.000**	0.223	0.053
UA (umol/L)	-0.023	0.671	0.125	0.020*	-0.067	0.215
GLU (mmol/L)	0.256	0.072	0.212	0.061	-0.065	0.260
LVMI (g/m^2)	0.681	0.000**	0.548	0.000**	-0.634	0.000**
LVEF (%)	-0.024	0.657	0.063	0.237	0.006	0.917
E/A<1 (%)	0.318	0.000**	0.317	0.000**	-0.422	0.000**
LA (mm)	0.586	0.000**	0.448	0.000**	-0.500	0.000**
LVEDD (mm)	0.459	0.000**	0.410	0.000**	-0.565	0.000**
IVST (mm)	0.640	0.000**	0.483	0.000**	-0.577	0.000**
LVPWT (mm)	0.640	0.000**	0.483	0.000**	-0.577	0.000**
BMI (kg/m^2)	0.101	0.060	0.048	0.375	-0.126	0.019*
Ang II (ng/L)	-	-	0.694	0.000**	-0.654	0.000**
ADM (ng/L)	0.694	0.000**	-	-	-0.678	0.000**
ADT (pg/mL)	-0.654	0.000**	-0.678	0.000**	-	-

*P<0.05, **P<0.01 means statistically significant. SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; UA, uric acid; LVEF, left ventricular ejection fraction; GLU, blood glucose; LVMI, left ventricular mass index; LA, left atrium; LVEDD, left ventricular end-diastolic pressure; IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; Ang II, angiotension II; ADM, adrenomedulin; ADT, adrenotensin.