ORIGINAL RESEARCH

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Plasma metanephrins are associated with myocardial hypertrophy and cardiac diastolic function in patients with essential hypertension

Abstract

Purpose: To explore the association between the sympathetic system activity and myocardial hypertrophy in patients with essential hypertension.

Methods: A total of 84 essential hypertension inpatients were recruited from China-Japan Friendship Hospital between January 2019 and September 2019. Activity of sympathetic system was quantified by plasma metanephrines (MNs) levels. All subjects received an echocardiographic test.

Results: The interventricular septum thickness (diastolic), left ventricular mass and left ventricular mass index increased significantly with plasma MNs quartiles, and plasma MNs were positively and significantly correlated with early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity.

Conclusions: In patients with essential hypertension, high level of plasma MNs associates with left ventricular hypertrophy and impaired diastolic function.

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Introduction

Hypertension can be defined as an elevated blood pressure of $\geq 140/90$ mmHg or reported current use of antihypertensive medications [1]. Essential hypertension, defined as high blood pressure in which secondary causes are excluded, accounts for 95% of all cases of hypertension [2]. Long term hypertension results in cardiac hypertrophy due to inevitable adaptation to increased hemodynamic load [3,4]. Hypertensive patients with left ventricular hypertrophy (LVH) are at high risk of developing rhythmic, mechanical and ischemic cardiac complications [5]. Reversal of LVH appears to be a desirable therapeutic goal in hypertensive patients to improve cardiovascular outcomes [6,7].

The sympathetic system is a highly versatile system whose functions are related to circulatory control, immune regulation, metabolism and emotion [8]. It has been shown that sympathetic overactivity plays an important role in the progression of hypertension and target organ damage. Previous studies have shown an association between increased cardiac sympathetic activity and hypertensive left ventricular (LV) hypertrophy in humans [9,10]. In the previous studies, evaluation of sympathetic activation was performed by measuring multiunit postganglionic sympathetic nerve activity, which reflects regional sympathetic activation only in cardiovascular system [9,10], or by mean heart rate, time domain heart rate variability (HRV) values, standard deviation of NN intervals, standard deviation of all five-minute NN intervals and triangular index, which were obtained from 24-hour electrocardiogram recordings and reflected sympathetic activation indirectly [11].

The metanephrines (MNs), including metanephrine (MN) and normetanephrine (NMN), are the *O*-methylated metabolites of epinephrine and norepinephrine, a process catalyzed by catechol-*O*-methyltransferase [12]. It has been reported that MNs were reliable markers of the whole sympathetic system activity [13]. In the present study, we aimed to investigate the association between plasma MNs and LVH, as well as cardiac diastolic function in patients with essential hypertension.

Methods

Study subjects

A total of 84 essential hypertension inpatients were recruited from China-Japan Friendship Hospital between January 2019 and September 2019. Essential hypertension was defined as blood pressure $\geq 140/90$ mmHg or previously diagnosed and current taking antihypertensive medication [1]. Causes of

secondary hypertension were ruled out based upon results of the following tests: serum and urinary electrolytes; plasma and urinary cortisol; plasma and urinary aldosterone; plasma renin activity; serum creatinine; plasma and urinary catecholamines; plasma and urinary MNs; thyroid stimulating hormone; free triiodothyronine and free thyroxine; Doppler studies of the renal arteries; and/or renal angiography.

The following patients were excluded from the study: patients with heart failure, myocardial infarction, angina pectoris and stroke; patients with serum creatinine >1.5 mg/dL; patients with atrial fibrillation or other major arrhythmias; patients with valvular heart disease; and pregnant or lactating patients.

Biochemical measurements

Plasma MNs were represented as plasma MN plus plasma NMN. Plasma MN and NMN were quantified by reverse-phase high-performance liquid chromatography (Agilent 1100 series, Santa Clara, CA) with electrochemical detection (ESA-A Dionex Company, Chelmsford, MA). The lowest detectable plasma MN concentration was 5 pg/mL and the lowest detectable plasma NMN concentration was 8 pg/mL.

Blood pressure was measured on the non-dominant arm, using an automated electronic device (OMRON Model1 Plus; Omron Company, Kyoto, Japan) in the seated position three times consecutively with 1-minute intervals after at least 5-minute rest. The average of three readings was used for analysis. The information about medical history, smoking and alcohol consumption were acquired. Current smoking or drinking status was defined as yes if the subject smoked or drank regularly in the past six months.

Ascertainment of LVH and left ventricular diastolic function

Principally, left ventricular hypertrophy is diagnosed by left ventricular mass (LVM) and left ventricular mass index (LVMI) via echocardiography [14]. Two-dimensional guided M-mode echocardiography was performed in all subjects. The LV end-diastolic internal dimension and wall thickness were measured according to the recommendations of the American Society of Echocardiography. The LV wall motion was evaluated by 2D and M-mode echocardiography images. Standard methods were used to calculate LV systolic fractional shortening and ejection fraction [15]. Left ventricular mass (LVM) was calculated from end-diastolic LV measurements by an anatomically validated formula: $LVM = (0.8 \times [1.04 \times 9 (LVDD + IVSTD + LVPWD)^3 - LVDD^3] + 0.6 \text{ g})$. The LVMI was calculated by dividing the LVM by the subject's body surface area (BSA) and was derived with

normal limits defined as 125 g/m² for men and 110 g/m² for women [16].

The following parameters were evaluated to assess left ventricular diastolic function: peak E velocity (early diastolic transmitral flow velocity); peak A velocity (late diastolic transmitral flow velocity); E/A ratio (early to late diastolic transmitral flow velocity); e' (early diastolic mitral annular tissue velocity); E/e' (early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity) [17]. All measurements of diastolic function were derived from the average of three consecutive cardiac cycles [18,19].

Statistical analysis

All statistical analyses were performed using SAS version 8.1 (SAS Institute, Cary, NC). Variables were presented as medians (interquartile ranges) or as number with proportion for categorical variables. The study population was divided into quartiles according to plasma MNs levels. For trend across quartiles, P was calculated by linear regression analysis for continuous variables and Cochran–Mantel–Haenszel for categorical variables.

Pearson correlation coefficients of plasma MNs with LVM, LVMI and E/e' were analyzed in unadjusted model. The multiple linear regression was used to investigate the associations of plasma MNs with LVM, LVMI and E/e' after adjusting for age, sex, body-mass index (BMI), systolic blood pressure (SBP), current smoking state and total cholesterol (TC) levels.

Linear regression analysis was used to investigate the association of plasma MNs with the area under the curve

(AUC) of LVM, LVMI and E/e', analysis of variance test and Bonferroni *post hoc* test were used for comparisons of the AUC of LVM, LVMI and E/e' in different plasma MNs quartiles.

Results

Characteristics of the study population

The clinical and biochemical characteristics of the study population in relation to plasma MNs quartiles are presented in Table 1. Percentage of patients with stage 3 hypertension ranges from 15% to 42.9% across plasma MNs quartiles. The IVSTd ranges from 7.52 (7.01-8.38) mm to 11.73 (8.66-13.64) mm across plasma MNs quartiles. The LV mass ranges from 156.05 (144.21-163.20) g to 221.46 (170.76-260.12) g across plasma MNs quartiles. The LVMI ranges from 105.22 (93.70-110.08) g/m² to 128.76 (112.45-133.67) g/m² across plasma MNs quartiles. Percentage of patients with stage 3 hypertension, IVSTd, LVM and LVMI significantly increased with plasma MNs quartiles (P=0.04, 0.02, 0.01 and 0.01, respectively; Table 1). As a marker of cardiac diastolic function, E/e' significantly increased from 9.12 (7.24-11.07) to 16.72 (12.05-20.31) with plasma MNs quartiles (P=0.001, Table 1). Using of beta receptor blockers significantly decreased from 80% to 33.3% across plasma MNs quartiles (P=0.03, Table 1). Other parameters were not statistically different among the plasma MNs quartiles.

TABLE 1. Clinical characteristics of the study population according to plasma metanephrens quartiles

Variables	MNs Quartiles (pg/ml)				P for trend
	Quartile 1 (46.2-89.7)	Quartile 2 (89.8-109.5)	Quartile 3 (109.6-135.3)	Quartile 4 (135.4-191.6)	
Patients, n	20	21	22	21	
Age, year	42.0 (24.0-60.0)	47.0 (28.0-56.0)	52.0 (35.0-60.0)	56.0 (42.0-63.0)	0.02
Male, n (%)	10 (50.0)	11 (52.4)	12 (54.5)	12 (57.1)	0.42
Current smoker, n (%)	4 (20.0)	4 (19.0)	5 (22.7)	6 (28.6)	0.49
Current drinker, n (%)	3 (15.0)	4 (19.0)	5 (22.7)	5 (23.8)	0.43
BMI (kg/m ²)	22.4 (20.3-24.8)	23.2 (21.6-24.5)	23.1 (21.7-25.3)	22.6 (20.6-24.2)	0.91
SBP, mmHg	140.3 (128.0-152.0)	142.5 (123.5-153.7)	143.4 (127.0-161.2)	141.7 (126.2-160.6)	0.72

DBP, mmHg	88.4 (78.6-98.0)	91.2 (80.5-100.2)	94.5 (81.4-105.8)	96.3 (83.6-107.4)	0.22
Hypertension stage 1, n(%)	11 (55.0)	9 (42.9)	7 (31.8)	4 (19.0)	0.21
Hypertension stage 2, n (%)	6 (30.0)	8 (38.1)	9 (40.9)	8 (38.1)	0.36
Hypertension stage 3, n (%)	3 (15.0)	4 (19.0)	6 (27.3)	9 (42.9)	0.04
TG, mmol/l	1.45 (1.05-1.96)	1.62 (1.14-2.05)	1.58 (0.99-2.25)	1.72 (1.15-2.37)	0.08
TC, mmol/l	4.03 (3.42-4.70)	4.12 (3.46-5.03)	4.08 (3.26-4.95)	4.46 (3.84-5.17)	0.34
LDL-C, mmol/l	2.51 (2.09-3.16)	2.64 (2.02-3.20)	2.77 (2.15-3.32)	2.85 (2.24-3.37)	0.41
HDL-C, mmol/l	1.26 (1.03-1.37)	1.30 (1.12-1.45)	1.19 (0.99-1.37)	1.23 (1.02-1.55)	0.35
ACEI, n (%)	9 (45.0)	12 (57.1)	10 (45.4)	9 (42.9)	0.18
Beta receptor blockers, n (%)	16 (80.0)	14 (66.7)	10 (45.4)	7 (33.3)	0.03
CCB, n (%)	15 (75.0)	13 (61.9)	17 (77.3)	16 (76.2)	0.35
Diuretic, n (%)	5 (25.0)	4 (19.0)	6 (27.3)	5 (23.8)	0.24
IVSTd, mm	7.52 (7.01-8.38)	9.10 (7.26-11.04)	10.24 (8.17-12.05)	11.73 (8.66-13.64)	0.02
LVM, g	156.05 (144.21-163.20)	173.43 (149.32-193.74)	193.54 (157.34-237.06)	221.46 (170.76-260.12)	0.01
LVMI, g/m ²	105.22 (93.70-110.08)	117.12 (97.93-128.45)	120.45 (107.35-130.26)	128.76 (112.45-133.67)	0.01
E/e'	9.12 (7.24-11.07)	11.56 (8.73-13.75)	14.49 (11.12-17.33)	16.72 (12.05-20.31)	0.001

Data are presented as median (interquartile ranges) or number (percentage).

Abbreviations: ACEI= angiotensin converting enzyme inhibitors; BMI=body mass index; CCB= calcium channel blocker; DBP=diastolic blood pressure; E/e'= early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity; HDL=high-density lipoprotein; IVSTd=interventricular septum thickness (diastolic); LDL=low-density lipoprotein; LVM= left ventricular mass; LVMI=left ventricular mass index; MNs indicates metanephrens; SBP=systolic blood pressure; TC=total cholesterol; TG=triglycerides.

Associations between plasma MNs and LVH

As shown in Table 2 and 3, plasma MNs were positively and significantly correlated with LVM and LVMI ($P=0.001$ and 0.003 , respectively). After adjusting for age, sex, BMI, SBP, current smoking state, TC, hypertension stage and using of beta blockers, the multivariable linear regression analysis also demonstrated that LVM and LVMI increased significantly with plasma MNs ($P=0.009$, $P=0.007$, respectively).

As shown in Figure 1A, patients with the highest plasma MNs quartile have significant higher LVM comparing to patients with lowest plasma MNs quartile (all $P<0.001$). The level of LVM increased significantly from the lowest plasma

MNs quartile to the plasma MNs highest quartile ($P<0.01$). The level of LVM in the fourth and the third plasma MNs quartiles were significantly higher compared to the lowest quartile ($P<0.001$, $P<0.001$, respectively).

As for the LVMI, the similar results were observed in Figure 1B. The level of LVMI increased significantly from the lowest plasma MNs quartile to the plasma MNs highest quartile ($P<0.01$). The level of LVMI in the fourth and the third plasma MNs quartiles were significantly higher compared to the lowest quartile ($P=0.003$, $P<0.001$, respectively).

TABLE 2. Associations analysis of plasma metanephrens with left ventricular mass

Variables	LVM (g)				
	Unadjusted			Adjusted	
	r	$\beta \pm SE$	P	$\beta \pm SE$	P
log MNs	0.277	0.703 $\pm$ 0.328	0.001	0.604 $\pm$ 0.509	0.009

Variables in adjusted models included age, sex, body mass index, systolic blood pressure, current smoking state, total cholesterol, hypertension stage and using of beta blockers.

Abbreviations: β , regression coefficient; log MNs, logarithmically transformed metanephrens; LVM, left ventricular mass; r, Pearson correlation coefficient; SE, standard error

TABLE 3. Associations analysis of plasma metanephrens with left ventricular mass index

Variables	LVMI (g)				
	Unadjusted			Adjusted	
	r	$\beta \pm SE$	P	$\beta \pm SE$	P
log MNs	0.340	2.997 $\pm$ 0.804	0.003	2.476 $\pm$ 0.744	0.007

Variables in adjusted models included age, sex, body mass index, systolic blood pressure, current smoking state, total cholesterol, hypertension stage and using of beta blockers.

Abbreviations: β , regression coefficient; log MNs, logarithmically transformed metanephrens; LVMI, left ventricular mass index; r, Pearson correlation coefficient; SE, standard error

Association between plasma MNs and left ventricular diastolic function

As shown in Table 4, plasma MNs were positively and significantly correlated with E/e' (P=0.002). After adjusting for age, sex, BMI, SBP, current smoking state, TC, hypertension stage and using of beta blockers, the multivariable linear regression analysis also demonstrated that E/e' increased significantly with plasma MNs (P=0.001).

As shown in Figure 2, patients with the highest plasma MNs quartile had significantly higher E/e' comparing with patients with lowest plasma MNs quartile (all P<0.001). The level of E/e' increased significantly from the lowest plasma MNs quartile to the highest quartile (P<0.001). The level of E/e' in the fourth and the third plasma MNs quartiles were significantly higher compared with the lowest quartile (P<0.001).

FIGURE 1A. AUC of LVM according to plasma MNs quartiles **FIGURE 1B. AUC of LVMI according to plasma MNs quartiles**

TABLE 4. Associations analysis of plasma metanephrins with early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity

Variables	E/e'				
	Unadjusted			Adjusted	
	r	$\beta \pm SE$	P	$\beta \pm SE$	P
log MNs	0.312	0.644 $\pm$ 0.219	0.002	0.578 $\pm$ 0.704	0.007

Variables in adjusted models included age, sex, body mass index, systolic blood pressure, current smoking state, total cholesterol, hypertension stage and using of beta blockers. Abbreviations: β , regression coefficient; log MNs, logarithmically transformed metanephrins; LVMI, left ventricular mass index; r, Pearson correlation coefficient; SE, standard error

FIGURE 2. E/e' according to plasma MNs quartiles

P values and P for trend were adjusted for age, sex, body mass index, systolic blood pressure, current smoking state, total cholesterol level, hypertension stage and the use of beta blockers. Abbreviations: AUC, area under curve; E/e', early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity; LVM, left ventricular mass; LVMI, left ventricular mass index; MNs, metanephrins;

Discussion

Left ventricular hypertrophy is an independent risk factor for major cardiac events. It increases morbidity and mortality in patients with hypertension [20]. Mechanical overload is the most important contributor to cardiac hypertrophy [20]. Elevated BP contributes to wall thickening and functional changes [9].

Although mechanical stress due to pressure overload is the major driver for LVH in patients with hypertension, it is currently recognized that neuro-hormonal abnormalities also play an important role. Neuro-hormonal substances, such as angiotensin II, aldosterone, norepinephrine and insulin, can directly promote myocyte hypertrophy and matrix deposition independent of their effects on systemic arterial pressure [21]. This could explain why, despite the successful lowering of SBP caused regression of LVH in a large proportion of SPRINT participants with baseline LVH (62% total; 70% in intensive arm, and 55% in standard arm), some patients still exhibited LVH [22].

Previous studies have revealed that the activation of sympathetic system was closely associated with hypertension. Masuo et al. [23] showed that increased baseline plasma norepinephrine concentration predicted elevated blood pressure over a 10-year follow-up. A clinical study indicated that a growth-promoting effect of high cardiac sympathetic activity on human myocardium was evident in the demonstrated proportionality between increased LV mass (normalized for blood pressure) and cardiac noradrenaline spillover in patients with essential hypertension [24].

In these previous studies, evaluation of sympathetic activation was performed by measuring multiunit postganglionic sympathetic nerve activity, which reflected regional sympathetic activation only in cardiovascular disease [9,10], or by means of heart rate and time domain heart rate variability values, standard deviation of NN intervals, standard deviation of all five-minute NN intervals and triangular index, which were obtained from 24-hour electrocardiogram recordings and reflected sympathetic activation indirectly [11]. Few studies have focused on the overall effect of sympathetic system activity on LV hypertrophy and LV diastolic function using serological methods.

In our study, we performed a retrospective study in patients with essential hypertension. We found IVSTd, LVM and LVMI were positively related to elevated plasma MNs, whereas left ventricular diastolic function was negatively associated with elevated plasma MNs. The activation of the sympathetic system was an important factor contributing to the LV hypertrophy and impaired diastolic function in essential hypertension.

Activation of the sympathetic system may be the common pathogenesis of elevated blood pressure and LV hypertrophy in patients with essential hypertension. Patients with essential hypertension had activated sympathetic system, showing by overproduction of catecholamines and their metabolites [25]. Long-term overproduction of catecholamines may result in chronic low-grade inflammation, which was presented as higher levels of inflammatory markers such as C-reactive protein, interleukin-1, interleukin-6 and tumor necrosis factor. These factors were found to be positively correlated with blood pressure [26] and LV hypertrophy [27,28].

According to the previous studies, factors inducing hypertensive LV hypertrophy may include increased cardiac, renal and muscle sympathetic nerve activity, leading to increased heart rate, cardiac output, renal vascular resistance and blood pressure. The increase in LV afterload induces adaptive cardiac structural changes, which are additionally potentiated in the presence of high norepinephrine levels or angiotensin II and finally culminate in a phenotype resembling LV hypertrophy. The sympathetic nervous system has been implicated in the development of cardiac hypertrophy, and cardiac sympathetic nerves were assumed to be the final common pathway in the induction of most types of hypertrophy [29]. Increased cardiac sympathetic neurotransmission has been suggested to contribute to the development of hypertrophy and alterations in cardiac adrenergic receptor function [29].

The use of adrenergic receptor blockers in hypertensive subjects demonstrated favorable effects on reversal of LV hypertrophy [30]. In our study, we found that in patients with essential hypertension, use of beta receptor blockers significantly decreased, from 80% to 33.3%, with plasma MNs quartiles. Most studies that included adrenergic receptor blockers revealed the ability of this drug class to reduce hypertensive LV hypertrophy beyond blood pressure-related effects [31,32]. Inhibiting sympathetic activation, such as central sympatholytic agents or β -blockers may prevent the occurrence of LV hypertrophy in patients with essential hypertension [33].

In conclusion, our study demonstrated in patients with essential hypertension, high level of plasma MNs was associated with LV hypertrophy and impaired diastolic function. Nevertheless, there were limitations that should be taken in consideration: this was a retrospective study, and the sample size was relatively small. Prospective studies with larger sample sizes should be performed to confirm our findings.

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