

## CASE STUDIES

# The relationship between left ventricular diastolic function and the autonomic nervous function in elderly patients with mild-to-moderate essential hypertension

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## ABSTRACT

**Objective:** To investigate the relationship between left ventricular diastolic function (LVDF) and autonomic nervous function in elderly patients with mild-to-moderate essential hypertension.

**Design:** A total of 146 elderly patients with mild-to-moderate essential hypertension were enrolled in our hospital from January, 2015 to October, 2017. Blood pressure was recorded, and biochemical indexes and the N-terminal pro-brain natriuretic peptide (NT-proBNP) were investigated. 2-dimensional echocardiography was used to measure the parameters of LVDF. Based on the classification standard of LVDF, all subjects were divided into two groups: normal LVDF group (n = 72), left ventricular diastolic dysfunction group (n = 74). At the same time, the dynamic electrocardiogram were investigated for all subjects to monitor the indexes of time on heart rate variability (HRV).

**Results:** (1) The level of NT-proBNP, left ventricular mass index (LVMI), interventricular septal thickness (IVST) and LVPWT increased significantly ( $p < .05$  for all), while the level of PNN50, rMSSD, SDANN and SDNN decreased significantly ( $p < .05$  for all) in left ventricular diastolic dysfunction group (abnormal LVDF group) compared with that in normal LVDF group (normal LVDF group); (2) The partial correlation analysis showed that rMSSD, PNN50 and triangle index were negatively correlated with peak A ( $r = -0.208, -0.219, -0.211, p < .05$  for all), and positive correlated with the ratio of peak E to peak A (E/A) ( $r = 0.179, 0.184, 0.181, p < .05$ ); SDNN were negatively correlated with NT-proBNP and E/E' ( $r = -0.183, -0.181, p < .05$  for all), positive correlated with E' ( $r = 0.178, p < .05$ ); (3) Multiple stepwise regression analysis showed that peak A and E/A were independent influencing factors for PNN50 ( $\beta = -0.261, p = .004; \beta = 0.179, p = .016$ ); E/E' and NT-proBNP were independent influencing factor for SDNN ( $\beta = -0.163, p = .018; \beta = -0.172, p = .022$ ).

**Conclusions:** Left ventricular diastolic dysfunction is closely related to impaired autonomic nervous function in elderly patients with mild-to-moderate essential hypertension.

**Key Words:** Mild-to-moderate essential hypertension, Autonomic nervous function, Left ventricular diastolic function

## 1. INTRODUCTION

Hypertension is a chronic disease that seriously threatens human health. It can cause damage to multiple organs such as the heart, brain and kidney. Studies had shown that the

occurrence and development of hypertension were closely related to autonomic nervous system function.<sup>[1]</sup> At present, there are few reports about the relationship between left ventricular diastolic function (LVDF) and autonomic nervous

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function in patients with mild-to-moderate essential hypertension, especially in elderly patients. The further study for relationship between target organ damage and autonomic nervous function has important clinical significance. Based on this, our study explored the relationship between LVDF and autonomic nervous function in elderly patients with mild-to-moderate essential hypertension by monitoring the indexes of autonomic nervous function, LVDF-related parameters<sup>[2-7]</sup> and detection of N-terminal pro-brain natriuretic peptide (NT-proBNP) which can more accurately and reasonably reflect the LVDF.<sup>[8-10]</sup>

## 2. MATERIALS AND METHODS

### 2.1 Subjects and study protocol

We selected 146 elderly patients with mild-to-moderate essential hypertension and only first stages of hypertension were enrolled in the Department of Cardiology, Civil Aviation General Hospital Beijing, PR China from January 2015 to October 2017. The diagnosis of elderly patients with essential hypertension is in line with the "2010 Guide to Prevention and Treatment of Hypertension in China".<sup>[11]</sup> That is, the patient is 65 years or older. Mild-to-moderate essential hypertension definition:  $140 \leq$  systolic blood pressure  $< 180$  mmHg and (or)  $90 \leq$  diastolic blood pressure  $< 110$  mmHg (1 mmHg = 0.133 kPa). All subjects were investigated by electrocardiogram and echocardiography, and underwent routine laboratory tests including fasting glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglycerides and creatinine by commercially available kits and a BECKMAN AU5800 automatic biochemical analyzer (United States). Plasma NT-proBNP was measured by enzyme-linked immunosorbent assay. Venous blood samples were drawn from all subjects in the morning after a fasting period of 12 hours. Body mass index (BMI) was calculated on the basis of weight in kilograms and height in square meter. The relevant data were recorded. All patients were excluded from the following patients: confirmed patients with systolic heart failure (left ventricular ejection fraction  $< 50\%$ ), Secondary hypertension, diabetes, coronary heart disease, heart failure and arrhythmia, cancer, liver and kidney dysfunction, chronic obstructive pulmonary disease (COPD) and asthma, pregnancy and peripheral vascular disease. All subjects had never received anti-hypertensive medication or had stopped taking all antihypertensive drugs for two or more weeks. All subjects were divided into two groups: 72 cases with normal LVDF group and 74 cases with left ventricular diastolic dysfunction (abnormal LVDF group) according to the results of LVDF assessment.

### 2.2 Ambulatory electrocardiogram monitoring

All patients were investigated by 24-hour ambulatory electrocardiogram monitor (model MIC-12H; shi ji jin ke medical devices Co, Ltd., Beijing, PR China). We adopted the analysis in time domain. Following parameters such as triangular index, standard deviation of all heart beat RR interval (SDNN), root mean square of adjacent RR intervals (RMSSD), standard deviation of all 5-minute beats RR interval mean (SDANN) and percentage of total beats of more than 50 ms between adjacent RR intervals (PNN50) were analyzed.

### 2.3 Echocardiography measurement

All subjects were investigated by echocardiography (GEVividE9, US), the probe frequency is of 1.7-3.4 MHz. The M-type, two-dimensional ultrasound and color Doppler echocardiography were performed to detect the following parameters: (1) routine parameters: interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular internal diameter end-diastolic (LVIDd), left ventricular internal diameter end-systolic (LVIDs), left atrium diameter (LAD); According to Devereux's formula:<sup>[6]</sup>  $LVM = 0.8 \times \{1.04 \times [(IVST + LVPWT + LVIDd)^3 - LVIDs^3]\} + 0.6$ , and left ventricular mass index (LVMI) =  $LVM / \text{body surface area}$ ; (2) Mitral spectral parameters: the peak value of blood flow velocity and the deceleration time of peak E (EDT) were measured in early diastole (E) and late diastole (A), and E/A was calculated; (3) Tissue Doppler parameters: the peak value of early diastolic velocity (E') was measured and the ratio of early diastolic velocity to annulus velocity E/E' was calculated; (4) Classification criteria of LVDF:<sup>[5]</sup> impaired relaxation function means that  $E/A < 0.8$ ,  $EDT > 200$  ms and  $E/E' \leq 8$ ; pseudo normalization means that E/A is 0.8-1.5, EDT is 160-200 ms and E/E' is 9-12; Limit filling means that  $E/A \geq 2$ ,  $EDT < 160$  ms and  $E/E' \geq 13$ . According to this criteria, all subjects were divided into normal LVDF group ( $n = 72$ ) and abnormal LVDF group ( $n = 74$ , only including patients with impaired relaxation or limited filling, because no pseudo normalization was found in all subjects in this study).

### 2.4 Statistical analysis

SPSS20.0 software package (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Data were expressed as mean  $\pm$  standard deviation. The *t*-test was used to compare the two groups. Categorical variables were compared among groups by  $\chi^2$  test. Non-normal distribution value of NT-proBNP was presented by using natural logarithmic conversion. Partial correlation analysis was used to analyze the relationship between LVDF and autonomic nervous function, NT-proBNP. Multivariate stepwise regression analysis was

used to analyze the influencing factors of autonomic nervous function.  $p < .05$  for the difference statistically significant.

**2.5 Clinical baseline characteristics**

Clinical baseline characteristics comparison: the differences of NT-proBNP between the two groups was statistically significant ( $p < .05$ ), while there were no significant difference in age, sex, BMI, blood pressure, smoking proportion, glucose, UA, creatinine, LDL-C, HDL-C, TC between two groups ( $p > .05$  for all). Results are shown in Tables 1-2.

**2.6 Characteristics of ambulatory electrocardiogram and echocardiography**

For the parameters of ambulatory electrocardiogram and echocardiography, LVMI, IVST and LVPWT were significantly increased in abnormal LVDF group compared with that in normal LVDF group ( $p < .05$  for all). Also, SDNN, PNN50, rMSSD and SDANN were decreased significantly compared with that in normal LVDF group ( $p < .05$  for all). There were no significant difference in the other parameters between the two groups. Results are shown in Table 3.

**Table 1.** Normal LVDF group clinical baseline characteristics ( $\bar{x} \pm s$ )

Group	Number of cases (men/women)	Age (year)	BMI (kg/m <sup>2</sup> )	SBP (mmHg)	DBP (mmHg)
Normal LVDF	72 (38/34)	68.0±3.2	21.61±1.06	163.56±5.84	90.64±5.85
Group	Smoking (%)	Heart rate (Times/min)	HDL-C (mmol/L)	LDL-C (mmol/L)	UA (mmol/L)
Normal LVDF	14 (9.6)	72.6±11.2	1.25±0.12	2.82±0.33	396.33±55.05
Group	Glucous (mmol/L)	TG (mmol/L)	TC (mmol/L)	Creatinine (μmol/L)	NT-proBNP (ng/L)
Normal LVDF	5.6±0.15	2.44±0.30	5.09±0.62	84±13	1.7±0.2

*Note.* Values are expressed as mean ±SD.  $p < .05$ , compared with Normal Group LVDF data. BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low density lipopro -tein cholesterol; TG: triglyceride; TC: total cholesterol; FBS: fasting blood sugar; UA: uric acid; SBP: systolic blood pressure; DBP: diastolic blood pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; LVDF: left ventricular diastolic function.

**Table 2.** Abormal LVDF group clinical baseline characteristics ( $\bar{x} \pm s$ )

Group	Number of cases (men/women)	Age (year)	BMI (kg/m <sup>2</sup> )	SBP (mmHg)	DBP (mmHg)
Abormal LVDF	74 (39/35)	70.5±3.3	22.43±0.61	168.88±10.45	92.06±4.80
Group	Smoking (%)	Heart rate (Times/min)	HDL-C (mmol/L)	LDL-C (mmol/L)	UA (mmol/L)
Abormal LVDF	16 (10.9)	73.3±11.1	1.22±0.13	2.93±0.40	415.31±57.39
Group	Glucous (mmol/L)	TG (mmol/L)	TC (mmol/L)	Creatinine (μmol/L)	NT-proBNP (ng/L)
Abormal LVDF	5.7±0.25	2.52±0.31	5.04±0.65	85±11	2.0±0.2 <sup>#</sup>

*Note.* Values are expressed as mean ±SD. <sup>#</sup>:  $p < .05$ , compared with Normal Group LVDF data. BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low density lipopro -tein cholesterol; TG: triglyceride; TC: total cholesterol; FBS: fasting blood sugar; UA: uric acid; SBP: systolic blood pressure; DBP: diastolic blood pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; LVDF: left ventricular diastolic function.

**Table 3.** Characteristics of ambulatory electrocardiogram and echocardiography ( $\bar{x} \pm s$ )

Group	PNN50 (%)	SDNN (ms)	rMSSD (ms)	SDANN (ms)	Triangular index
Abormal LVDF	11.2±4.1 <sup>#</sup>	81.3±14.1 <sup>#</sup>	23.8±5.1 <sup>#</sup>	87.8±16.1 <sup>#</sup>	21.7±2.9
Normal LVDF	14.8±6.2	114.9±18.8	30.7±7.5	119.1±18.4	24.6±2.7
Group	LVMI (g/m <sup>2</sup> )	IVST (mm)	LVPWT (mm)	LAD (mm)	EF (%)
Abormal LVDF	90.9±18.5 <sup>#</sup>	8.9±1.2 <sup>#</sup>	8.7±1.2 <sup>#</sup>	32.3±2.7	66.4±5.9
Normal LVDF	82.2±14.1	8.0±1.1	8.0±1.3	33.5±2.6	67.6±6.1

*Note.* Values are expressed as mean ±SD. <sup>#</sup>:  $p < .05$ , compared with Normal LVDF Group data. SDANN: standard deviations of the averages of RR intervals in all 5-minute segments of the entire recording; PNN50: percentage of total beats of more than 50ms between adjacent RR intervals; SDNN: standard deviations of all RR intervals; average normal RR interval standard deviation; rMSSD: Root mean square of adjacent RR intervals; LVMI: Left ventricular mass index; IVST: interventricular septal thickness; LVPWT: Left ventricular posterior wall thickness; LAD: Left atrial diameter; EF: Ejection fraction; LVDF: Left ventricular diastolic function.

## 2.7 Relationship between change in echocardiography parameters, NT-proBNP and ambulatory electrocardiogram

Partial correlation analysis showed the following: PNN50, triangular index and rMSSD were negatively correlated with peak A, and positively correlated with E/A ( $p < .05$  for all); SDNN were positively correlated with E', and negatively correlated with E/E' and NT-proBNP ( $p < .05$  for all). Results are shown in Table 4.

## 2.8 Multivariate stepwise regression analysis for autonomic nervous function: Association with influence factors

We took autonomic nervous function index as the dependent variable, and LVDF parameters, NT-proBNP as independent variables for multivariate stepwise regression analysis. Results showed that E/E' and NT-proBNP were significantly correlated with SDNN ( $p < .05$  for all). Peak A and E/A were significantly correlated with PNN50 ( $p < .05$  for all). Results are shown in Table 5.

**Table 4.** Partial correlation analysis (n = 146)

Parameters	Triangular index	SDANN	SDNN	rMSSD	PNN 50%
E	0.009	-0.005	-0.024	0.010	0.006
A	-0.211 <sup>#</sup>	-0.089	-0.070	-0.208 <sup>#</sup>	-0.219 <sup>#</sup>
E/A	0.181 <sup>#</sup>	0.109	0.120	0.179 <sup>#</sup>	0.184 <sup>#</sup>
E'	0.101	0.147	0.178 <sup>#</sup>	0.111	0.085
E/E'	-0.061	-0.142	-0.181 <sup>#</sup>	-0.071	-0.059
EDT	0.064	0.124	0.152	0.041	-0.001
NT-proBNP	-0.122	-0.109	-0.183 <sup>#</sup>	-0.148	-0.139

*Note.* The values in the table are partial correlation coefficients(r). SDANN: standard deviations of the averages of RR intervals in all 5-minute segments of the entire recording; PNN50: percentage of total beats of more than 50ms between adjacent RR intervals; E: transmitral diastolic early peak inflow velocity; A: transmitral diastolic late inflow flow; E': early diastolic velocities of mitral annulus; EDT: the deceleration time of peak E; SDNN: standard deviations of all RR intervals; average normal RR interval standard deviation; rMSSD: Root mean square of adjacent RR intervals; NT-proBNP: N-terminal pro-brain natriuretic peptide. <sup>#</sup>:  $p < .05$ .

**Table 5.** Multivariate stepwise regression analysis

Dependent variable	Independent variable	Standard error	$\beta$	t value	p value
SDNN	E/E'	0.176	-0.163	-2.391	.018
	NT-proBNP	1.912	-0.172	-2.313	.022
PNN50	peak A	0.088	-0.261	-2.919	.004
	E/A	0.015	0.179	2.369	.016

*Note.* SDANN: Standard deviation of mean RR intervals per 5-minute beats; PNN50: percentage of adjacent RR intervals that differ by > 50 ms as a percentage of the total number of RR intervals; E: transmitral diastolic early peak inflow velocity; A: transmitral diastolic late inflow flow; E': early diastolic velocities of mitral annulus; EDT: the deceleration time of peak E; NT-proBNP: N-terminal pro-brain natriuretic peptide.

## 3. DISCUSSION

Essential hypertension is closely related to cardiac autonomic nervous function. Due to the loss of autonomic nervous function balance, the excessive activation of sympathetic nerve was often found in patients with essential hypertension. Studies had shown that:<sup>[12-14]</sup> the unbalanced autonomic nerve function is closely related to the target organ damage including LVDF in patients with early and late essential hypertension. At present, the epidemiological material showed<sup>[15-17]</sup> that the patients with LVDF were often found among those patients with essential hypertension, obesity or diabetes. Left ventricular diastolic dysfunction can result in circulatory dysfunction due to impaired voluntary relaxation of the Left

ventricle or decreased compliance.<sup>[18,19]</sup> In addition, studies<sup>[20,21]</sup> had shown that NT-proBNP is superior to systolic function in evaluating diastolic function. NT-proBNP abnormalities can still be investigated in patients with left ventricular diastolic dysfunction due to the long half-life of NT-proBNP. In this study, we investigated routine and LVDF by using echocardiography and measuring NT-proBNP. The results in this study showed that NT-proBNP, LVMI, IVST and LVPWT were significantly increased in patients with left ventricular diastolic dysfunction as compared with those in normal LVDF, indicating that there were cardiac structure changes while accompanied by left ventricular diastolic dysfunction in elderly patients with mild to moderate essential hypertension.

heart rate variability (HRV) refers to the small differences in sequential heart beat, which essentially reflect the sympathetic and parasympathetic regulatory effects on the sinus node and the functional status of autonomic nervous system of heart. Also, HRV is also a relatively independent and correlated indicator to judge the prognosis of cardiovascular disease.<sup>[22-24]</sup> HRV markers include SDANN reflecting the sympathetic nerve activity, rMSSD, and PNN50 reflecting the parasympathetic activity as well as SDNN reflecting a whole autonomic nervous function. In this study, we used ambulatory electrocardiography to examine the autonomic nervous function. The results showed that SDNN, SDANN, PNN50 and rMSSD were significantly lower in abnormal LVDF group than in normal LVDF group, indicating that hypertensive patients with left ventricular diastolic dysfunction had the increased sympathetic nerve excitability. Partial correlation analysis showed that LVDF index including E', E/E', E/A, A peak was significantly associated with SDNN, SDANN and PNN50; Further stepwise multiple regression analysis showed that NT-proBNP, E/E' are independent factors of SDNN, and E' and E/A are independent influencing factors of PNN50, indicating that autonomic nervous function is closely related to LVDF in elderly patients with mild to moderate essential hypertension. Thus, our study also suggested that elderly hypertensive patients with left ventricular diastolic dysfunction were accompanied by increased sympathetic nerve activity and impaired vagal function and aggravated with the damage of target organs. Therefore, the treatment of elderly hypertensive patients should focus on regulating vagal function so as to facilitate the improvement of prognosis. In addition, the study<sup>[25]</sup> found that both rMSSD and PNN50 were decreased among those healthy people with E/A < 1, and thus further demonstrated that left ventricular diastolic dysfunction was often accompanied by impairment of parasympathetic function. The possible cause is the effect of left atrial volume on autonomic nervous function. The volume receptors which locate in left atrium can modulate the function of sympathetic and parasympathetic nerve. While left atrial volume increase, sympathetic nerve activity reduce and parasympathetic nerve activity increase. For maintaining the total filling quantity of left ventricle, left atrium need to contract more strongly due to the attenuation

of myocardial positive relaxation of left ventricle. Thus, the effect of left atrial volume on parasympathetic nerve is attenuated relatively, that is to say that parasympathetic nerve activity reduce.

The major limitations of our study were that first, the small sample size limited the statistical power to explore the relationship between LVDF and the autonomic nervous function in elderly patients with mild-to-moderate essential hypertension, second, our study did not include all kinds of left ventricular diastolic dysfunction due to a small number of patients.

In conclusion, left ventricular diastolic dysfunction is associated with impairment of autonomic nervous system in elderly patients with mild-to-moderate essential hypertension. As we know, the hypertensive patients with heart failure often accompanied by malignant arrhythmia which is an important cause of sudden cardiac death.<sup>[26]</sup> Early improvement of left ventricular diastolic dysfunction can delay the progression of heart failure and have a positive effect on the prognosis of patients.<sup>[27]</sup> The combined monitoring of dynamic electrocardiogram and echocardiography can not only reflect the autonomic nervous function, but also is a screening way to identify left ventricular diastolic dysfunction in elderly patients with mild-to-moderate essential hypertension. Thus, it has important clinical significance in the guidance of clinical treatment. For the clinical treatment of elderly hypertensive patients with left ventricular diastolic dysfunction, it should be emphasized that, on the basis of improvement of their life style,  $\beta$ -blockade need to be taken if there are no contraindications because of the better effect of  $\beta$ -blockade on left ventricular diastolic dysfunction and HRV.<sup>[28,29]</sup>

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## CONFLICTS OF INTEREST DISCLOSURE

The authors report no conflicts of interest in this study.

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