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RESEARCH ARTICLE

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Correlation between catecholamines and echocardiographic parameters in patients with pheochromocytoma and paraganglioma

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Abstract

Purpose: To analyze the correlation between catecholamines and echocardiographic parameters in patients with pheochromocytoma and paraganglioma (PPGL).

Methods: Sixty-six patients who underwent surgical resection of pathologically proven PPGL from January 2016 to June 2019 were examined. Echocardiographic parameters were compared between patients with elevated catecholamine concentrations and those with normal concentrations.

Results: The percentage of patients with elevation of any catecholamine (NE, DA, or E, and their metabolites) did not significantly differ between patients with normal and abnormal left ventricular ejection function (LVEF) or diastolic function (LVDF). E wave deceleration time (EDT) was significantly lower in patients with elevation of any catecholamine than in those with normal concentrations ($p = 0.024$). EDT was significantly lower in patients with elevated NE and its metabolites than in patients with normal NE concentration ($p = 0.004$). After adjusting for gender and age, EDT was significantly negatively correlated with elevated NE and its metabolites in regression analysis (B-value, -39.853; $p = 0.023$) and correlation analysis ($r = -0.349$; $p = 0.004$).

Conclusion: NE and its metabolites may have an impact on left ventricular diastolic function, which can be reflected by EDT. EDT was negatively correlated with elevated NE and its metabolites.

KEYWORDS
catecholamines, echocardiography, E-wave deceleration time, left ventricular diastolic function, paraganglioma, pheochromocytoma

1 | BACKGROUND

Pheochromocytoma and paraganglioma (PPGL) are neuroendocrine tumors that arise from cells derived from the embryonic neural crest and can synthesize and secrete large amounts of catecholamines. Catecholamine release may cause a sudden increase in blood pressure resulting in organ damage or even death. An autopsy study reported myocardial damage in 58% of PPGL patients. In addition, hypercatecholaminemia can directly cause myocardial damage, fibrosis, ischemia, and arrhythmia.[1] Elevated concentrations of catecholamines are

an important cause of cardiac hypertrophy in patients with PPGL, independent of hypertension.[2] This study aimed to examine the correlation between catecholamines and echocardiographic parameters that indicate cardiac damage in patients with PPGL.

2 | METHODS

A total of 147 patients who underwent surgical resection of presumed PPGL from January 2016 to June 2019 were eligible for study inclusion. The following data were recorded: gender, age, height, weight, medical history, medication, tumor volume, tumor malignancy, and preoperative catecholamine concentrations. Echocardiographic imaging acquisition and assessment were performed by experienced physicians according to standardized guidelines. Interventricular septum (IVS) thickness, left ventricular posterior wall (LVPW) thickness, left ventricular internal dimension in diastole (LVIDd), left ventricular internal dimension in systole (LVIDs) and left ventricular mass index (LMI) were recorded as parameters reflecting left ventricular morphology. Left ventricular ejection fraction (LVEF) was recorded as a measure of overall left ventricular systolic function, and s' of the mitral valve septum annulus as a reflection of left ventricular long axis motion ability. As parameters related to left ventricular diastolic function (LVDF), left atrial volume index (LAVI), mitral valve E peak flow rate, E/A ratio, E wave deceleration time (EDT), interventricular septum e', E/e' ratio, and tricuspid regurgitation maximum flow rate (TRmax) were recorded. Figure 1 shows the measurement of EDT. Based on the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines,[3] LVDF was considered abnormal when more than two of the following were present: LAVI >34 ml/m^2, septum e' < 7 cm/s, E/e' ratio > 14, and TRmax >280 cm/s. LVEF <50% was considered abnormal. Catecholamine concentration elevation was defined according to reference ranges used by local testing laboratory (the patients came from all over the country): a measured concentration that exceeded the normal reference range was considered elevated.

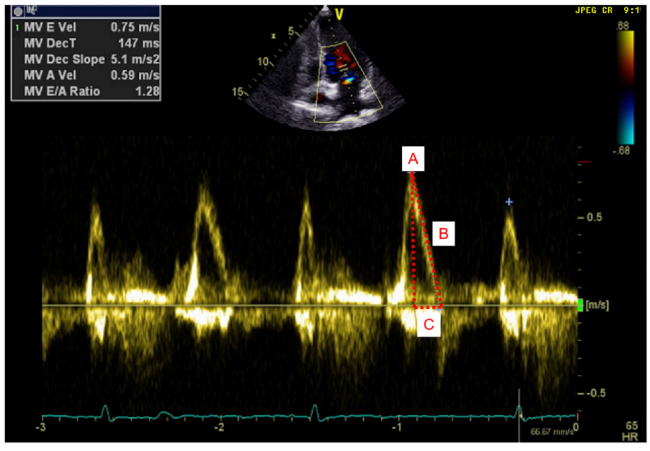

FIGURE 1 Measurement of EDT. (A) E-wave velocity. (B) Deceleration slope. and (C) E wave deceleration time (EDT)

TABLE 1 Patient characteristics

Basic data	
Gender (M/F)	30/36
Age	47.02 ± 16.03
BMI (kg/m^2)	22.92 ± 3.02
History of hypertension (months)	21.38 ± 31.06
Maximum SBP recorded (mmHg)	191.98 ± 30.79
Maximum DBP recorded (mmHg)	110.72 ± 22.09
Minimum SBP recorded (mmHg)	127.82 ± 13.56
Minimum DBP recorded (mmHg)	78.95 ± 11.27
SBP at admission (mmHg)	125.97 ± 15.66
DBP at admission (mmHg)	76.92 ± 9.80
Taking antihypertensive drugs before admission *n* (%)	51 (77.27)
Tumor volume (cm^3)	76.29 ± 117.96
Malignant tumor *n* (%)	37 (56.06%)
Echocardiographic parameters	
LVEF(%)	68.54 ± 8.26
LVEF<50% *n* (%)	4 (6.06%)
Abnormal LVDF *n* (%)	9 (13.64%)
Septum e' (cm/s)	7.48 ± 2.26
Septum s' (cm/s)	8.65 ± 1.61
E/e'	11.10 ± 3.50
EDT (ms)	182.80 ± 54.02
LAVI (ml/m^2)	25.25 ± 7.81
IVS (cm)	0.95 ± 0.15
LVPW (cm)	0.93 ± 0.14
LVIDd (cm)	4.44 ± 0.42
LVIDs (cm)	2.70 ± 0.43
LVMI (g/m^2)	83.71 ± 21.28
Any catecholamines elevation, *n* (%)	58 (87.88%)
NE and its metabolites elevation, *n* (%)	55 (83.33%)
DA and its metabolites elevation, *n* (%)	2 (3.03%)
E and its metabolites elevation, *n* (%)	22 (33.33%)

Abbreviations: BMI, body mass index; DA, dopamine; DBP, diastolic blood pressure; E, epinephrine; EDT, E wave deceleration time; IVS, interventricular septum thickness; LAVI, left atrial volume index; LVDF, left ventricular diastolic function; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall thickness; LVIDd, left ventricular internal dimension diastole; LVIDs, left ventricular internal dimension systole; LVMI, left ventricular mass index; NE, norepinephrine; SBP, systolic blood pressure.

Statistical analyses were performed using SPSS software version 22 (IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution are expressed as means with standard deviation; those with a non-normal distribution are expressed as medians with interquartile range. Categorical variables are expressed as numbers with percentage. The independent samples t-test, analysis of variance, Kruskal–Wallis rank-sum test, and chi-square test were used as appropriate to compare variables between groups. Relationships between

catecholamine elevation and echocardiographic parameters were evaluated using linear regression and correlation analysis. Inter-observer agreement was evaluated using the kappa statistic (poor, $\kappa \leqq 0.40$; moderate, $0.40 < \kappa \leqq 0.60$; good, $0.60 < \kappa \leqq 0.80$; and excellent, $\kappa > 0.80$).

3 | RESULTS

3.1 | Clinical characteristics

Among the 147 eligible patients, four who had a final pathological diagnosis other than PPGL were excluded. We also excluded 43 in whom echocardiography testing was inadequate or not available and 34 in whom catecholamine testing was not available. Finally, 66 patients were included for analysis. Mean age was 47.02 years and 36 were women. Preoperative LVEF was abnormal in four and LVDF was abnormal in nine. Three patients had both decreased LVEF and abnormal LVDF. Catecholamines were elevated above normal concentrations in 58 patients (some patients had elevation of more than one catecholamine). Norepinephrine (NE) and its metabolites were elevated in 55, dopamine (DA) and its metabolites in two, and epinephrine (E) and its metabolites in 22. Fifty-one patients were taking antihypertensive drugs; 29 were taking an α-receptor blocker. Patient characteristics are shown in Table 1.

3.2 | Association of catecholamine elevation with left ventricular function

The percentage of patients with elevation of any catecholamine (NE, DA, or E and its metabolites) did not significantly differ between patients with normal and abnormal LVEF or LVDF (Table 2).

3.3 | Correlation between catecholamine elevation and echocardiographic parameters

EDT was significantly lower in patients with elevation of any catecholamine concentration than in those with normal concentrations ($p = 0.024$; Table 3). EDT was significantly lower in patients with elevated NE and its metabolites concentration than in patients with normal NE and its metabolites concentration ($p = 0.004$). After adjusting for gender and age, EDT was negatively correlated with elevated NE and its metabolites concentration ($r = -0.349$; $p = 0.004$; Table 4).

3.4 | Inter-observer agreement

Inter-observer agreement was excellent for septum s', E/e', IVS, LVIDd and LVDF (κ-value = 0.854, 0.847, 0.820, 0.926, and 0.842, respectively; $p < 0.001$); good for EDT and LVIDs (κ-value = 0.789 and 0.775, respectively, $p < 0.001$); and moderate for LVPW (κ-value = 0.483, $p < 0.001$).

4 | DISCUSSION

In this study, the percentage of patients with elevated catecholamines has no significant difference between patients with normal and abnormal LVEF. Because of the small sample size of this study, the number of patients with impaired left ventricular function was very small (only 4 of 66 people had reduced LVEF), which may have introduced bias. However, theoretically, PPGL releases catecholamines that have a direct effect on the myocardium through mechanisms such as calcium overload, cell membrane permeability changes, and increased lipid fluidity. These may result in abnormal cardiac structure and function.[4–6] In addition, catecholamines and their oxidative metabolites can indirectly damage the myocardium by inducing coronary spasm, myocardial ischemia, and arrhythmia, which then can alter cardiac structural and functional abnormalities.[7] Mitral ventricular septum s', another parameter that reflects ventricular systolic performance, did not significantly differ between patients with elevation of any catecholamine and those with normal concentrations. This indicates that the effect of catecholamines on left ventricular systolic function is not reflected by left ventricular shortening. The percentage of patients with elevation of any catecholamine did not significantly differ between the normal and abnormal LVDF groups; however, EDT did. This suggests that the catecholamine effect on overall left ventricular

TABLE 2 Catecholamines elevation in patients grouped according to left ventricular ejection fraction and diastolic function

	Normal LVEF ($n = 62$)	Reduced LVEF ($n = 4$)	p-value	Normal LVDF ($n = 57$)	Abnormal LVDF (n = 9)	p-value
Any catecholamine elevation n (%)	54 (87.10%)	4 (100%)	0.443	51 (89.47%)	7 (77.78%)	0.318
NE and its metabolites elevation n (%)	51 (82.26%)	4 (100%)	0.356	48 (84.21%)	7 (77.78%)	0.630
DA and its metabolites elevation n (%)	2 (5.88%)	0 (0%)	0.715	2 (3.51%)	0 (0%)	0.568
E and its metabolites elevation n (%)	21 (33.87%)	1 (25%)	0.715	19 (33.33%)	3 (33.33%)	1.000

Abbreviations: DA, dopamine; E, epinephrine; LVEF, left ventricular ejection fraction; LVDF, left ventricular diastolic function; NE, norepinephrine.

TABLE 3 Echocardiographic parameters in patients with elevated catecholamine concentrations and those with normal concentrations

Echocardiographic parameters	LAVI (ml/m^2)	LVEF (%)	Septum e' (cm/s)	Septum s'(cm/s)	E/e'	EDT (ms)	IVS (cm)	LVPS (cm)	LVIDd (cm)	LVIDs (cm)	LVMI (g/m^2)
CAT (+) ($n = 58$)	25.03 ± 7.75	68.45 ± 8.64	7.67 ± 2.309	8.71 ± 1.54	10.95 ± 3.51	177.28 ± 53.95	0.95 ± 0.15	0.93 ± 0.14	4.44 ± 0.43	2.69 ± 0.45	83.70 ± 21.80
CAT (−) ($n = 8$)	26.80 ± 8.64	69.17 ± 4.98	6.16 ± 1.32	8.23 ± 2.18	12.10 ± 3.43	222.79 ± 36.25	0.97 ± 0.12	0.97 ± 0.14	4.46 ± 0.34	2.74 ± 0.33	83.75 ± 18.28
p-value	0.552	0.818	0.078	0.434	0.389	**0.024**	0.631	0.491	0.877	0.771	0.995
NE (+) ($n = 55$)	25.14 ± 7.78	68.75 ± 8.75	7.73 ± 2.32	8.71 ± 1.57	10.90 ± 3.51	174.43 ± 52.17	0.94 ± 0.15	0.93 ± 0.14	4.43 ± 0.44	2.69 ± 0.45	83.64 ± 22.17
NE (−) (n = 11)	25.83 ± 8.39	67.49 ± 5.36	6.27 ± 1.49	8.32 ± 1.88	12.02 ± 3.42	224.65 ± 44.22	0.99 ± 0.11	0.96 ± 0.12	4.47 ± 0.29	2.72 ± 0.30	84.05 ± 16.99
p-value	0.800	0.649	0.051	0.463	0.340	**0.004**	0.337	0.504	0.783	0.850	0.955
DA (+) ($n = 2$)	23.71 ± 1.84	66.30 ± 2.26	12.10 ± 1.27	10.65 ± 0.35	9.20 ± 0.000	114.40 ± 54.87	0.98 ± 0.03	1.00 ± 0.00	4.55 ± 0.21	2.80 ± 0.14	88.81 ± 9.65
DA (−) ($n = 64$)	25.29 ± 7.93	68.55 ± 8.39	7.33 ± 2.13	8.59 ± 1.60	11.16 ± 3.54	184.93 ± 53.01	0.95 ± 0.15	0.93 ± 0.14	4.44 ± 0.42	2.69 ± 0.44	83.55 ± 21.56
p-value	0.781	0.967	**0.003**	0.075	0.440	0.069	0.772	0.500	0.709	0.731	0.733
E (+) ($n = 22$)	26.91 ± 8.72	68.69 ± 7.63	6.93 ± 2.13	8.62 ± 1.74	11.09 ± 4.39	187.32 ± 65.60	0.96 ± 0.17	0.96 ± 0.14	4.37 ± 0.50	2.65 ± 0.48	84.65 ± 21.32
E (−) ($n = 44$)	24.45 ± 7.32	68.46 ± 8.64	7.77 ± 2.30	8.66 ± 1.57	11.10 ± 2.99	180.54 ± 47.89	0.95 ± 0.13	0.92 ± 0.14	4.48 ± 0.37	2.72 ± 0.41	83.24 ± 21.49
p-value	0.240	0.916	0.162	0.923	0.994	0.634	0.776	0.354	0.350	0.549	0.802

Abbreviations: CAT (+), any catecholamine elevation; CAT (−), any catecholamine not elevation; DA (+), DA and its metabolites elevation; DA (−), DA and its metabolites not elevation; DA, dopamine; E (+), E and its metabolites elevation; E (−), E and its metabolites not elevation; EDT, E wave deceleration time; E, epinephrine; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; IVS, interventricular septum thickness; LVPW, left ventricular posterior wall thickness; LVIDd, left ventricular internal dimension diastole; LVIDs, left ventricular internal dimension systole; LVMI, left ventricular mass index; NE (+), NE and its metabolites elevation; NE (−), NE and its metabolites not elevation; NE, norepinephrine.

Note: Bold values mean that these values are less than 0.05.

diastolic function may be reflected in the specific ultrasonic parameters.

Movement in the long-axis direction of the left ventricle is mainly completed by the inner myocardium. Abnormal function of the inner myocardium is reflected as abnormal diastolic function. Echocardiographic indicators of diastolic dysfunction include e' reduction and EDT shortening. Diastolic performance (rather than global LV function) is usually the first to decline in the early stages of cardiac damage. EDT is mainly affected by left ventricular relaxation, left ventricular diastolic pressure and compliance and reflects LVDF to a certain extent. Its measurement is feasible and repeatable. EDT shortening can indicate increased left ventricular stiffness and left ventricular end diastolic pressure. Previous studies have confirmed that EDT can provide prognostic information, as can clinical indicators, ventricular wall motion and LVEF.[8–13] In patients with acute myocardial infarction and heart failure with low EF, EDT shortening has been associated with heart failure symptoms, mortality, and hospitalization. In our study, mean EDT was 182.80 ± 54.02 ms and elevated NE and its metabolites was negatively correlated with EDT; however, the correlation was weak. In any case, echocardiography is important in PPGL patients as it can provide important data to guide management and determine prognosis.

4.1 | Limitations

This study has several limitations. All patients in this study had a history of hypertension, but they were not analyzed according to cause (catecholamines, other secondary factors, primary hypertension, or a combination); however this is the situation in real-world management of PPGL patients. In a previous study,[2] elevated catecholamines were considered the cause of cardiac hypertrophy in patients with pheochromocytoma, independent of hypertension. Although we cannot currently distinguish the effects of hypertension and PPGL on the myocardium, we can conclude that catecholamines have an adverse impact on myocardial diastolic function in PPGL patients. We also selected many echocardiographic parameters that reflect left ventricular systolic and diastolic function but did not include indicators that reflect left ventricular strain. This was because different ultrasound machines were used to examine our patients, and we did not have corresponding software to process strain information. Because there were few patients with simple primary hypertension in the same period, it was difficult to set up a control group. Future case-control studies are warranted.

The use of different machines and the fact that the physicians performing echocardiography were not blinded to the clinical data may have introduced bias; however, the physicians were experienced and used standardized guidelines, and inter-observer agreement was good or excellent for most echocardiographic data. Therefore, we believed the data was accurate.

TABLE 4 Regression analysis of catecholamines and echocardiographic parameters[a]

Echocardiographic parameters	Regression			Correlation		
	Catecholamine	*B*-value	95%CI	*p* value	*r*-value	*p*-value
EDT	NE (+)	−39.853	−74.097, −5.609	0.023	−0.349	**0.004**
	DA (+)	−51.835	−127.020, 23.350	0.173	−0.226	0.069
	E (+)	−2.160	−30.317, 25.998	0.879	0.060	0.634
	CAT (+)	−35.260	−74.338, 3.817	0.076	−0.277	**0.024**

Abbreviations: CAT (+), any catecholamine elevation; CI, confidence interval; DA (+), DA and its metabolites elevation; EDT, E wave deceleration time; E (+), E and its metabolites elevation; NE (+), NE and its metabolites elevation.
Note: Bold values mean that these values are less than 0.05.
[a]Adjusted for gender and age.

5 | CONCLUSION

NE and its metabolites may have an impact on left ventricular diastolic function, which can be reflected by EDT. EDT was negatively correlated with elevated NE and its metabolites.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Research data are not shared." cd_value_code="text

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REFERENCES

1. Expert consensus on the diagnosis and treatment of pheochromocytoma and paraganglioma(2020). *Chin J Endocrinol Metab*. 2020;36(9):737-750.
2. Li D. A clinical study of cardiovascular manifestations of pheochromocytoma. Peking Union Medical College; 2013.
3. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.
4. Deegan RJ, Furman WR. Cardiovascular manifestations of endocrine dysfunction. *J Cardiothorac Vasc Anesth*. 2011;25(4):705-720.
5. Prejbisz A, Lenders JWM, Eisenhofer G, Januszewicz A. Cardiovascular manifestations of phaeochromocytoma. *J Hypenens*. 2011;29(11):2049-2060.
6. Shub C, Cueto-Garcia L, Sheps SG, Ilstrup DM, Tajik AJ. Echocardiographic findings in pheochromocytoma. *Am J Cardiol*. 1986;57(11):971-975.
7. Hassan Y, Falhammar H. Cardiovascular manifestations and complications of pheochromocytomas and paragangliomas. *J Clin Med*. 2020;9((8)):2435.
8. Rihal CS, Nishimura RA, Hatle LK, Bailey KR, Tajik AJ. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy. *Relat Sympt Prognosis Circul*. 1994;90(6):2772-2779.
9. Giannuzzi P, Temporelli PL, Bosimini E, et al. Independent and incremental prognostic value of Doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. *J Am Coll Cardiol*. 1996;28(2):383-390.
10. Hurrell DG, Oh JK, Mahoney DW, Miller FA Jr, Seward JB. Short deceleration time of mitral inflow E velocity: prognostic implication with atrial fibrillation versus sinus rhythm. *J Am Soc Echocardiogr*. 1998;11(5):450-457.
11. Andersson C, Gislason GH, Weeke P, et al. EchoCardiography and heart outcome study (ECHOS) investigators. The prognostic importance of a history of hypertension in patients with symptomatic heart failure is substantially worsened by a short mitral inflow deceleration time. *BMC Cardiovasc Disord*. 2012;25(12):30.
12. Palmiero P, Zito A, Maiello M, et al. Left ventricular diastolic function in hypertension: methodological considerations and clinical implications. *J Clin Med Res*. 2015;7(3):137-144.
13. Xin Y, Hu W, Chen X, Hu J, Sun Y, Zhao Y. Prognostic impact of light-chain and transthyretin-related categories in cardiac amyloidosis: a systematic review and meta-analysis. *Hellenic J Cardiol*. 2019;60((6)):375-383.

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