

PREVALENCE AND PATTERNS OF LEFT VENTRICULAR DYSFUNCTION IN PATIENTS WITH PHEOCHROMOCYTOMA

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BACKGROUND: Excessive catecholamine release in pheochromocytoma is known to cause transient reversible left ventricular (LV) dysfunction, such as in the case of pheochromocytoma-associated catecholamine cardiomyopathy. We investigated patterns of clinical presentation and incidence of LV dysfunction in patients with pheochromocytoma.

METHODS: From January 2004 to April 2011, consecutive patients with pheochromocytoma were retrospectively studied with clinical symptoms, serum catecholamine profiles, and radiologic findings. Patterns of electrocardiography and echocardiography were also analyzed.

RESULTS: During the study period, a total of 36 patients (21 males, 49.8 ± 15.8 years, range 14-81 years) with pheochromocytoma were included. In the electrocardiographic examinations, normal findings were the most common findings (19, 52.8%). LV hypertrophy in 12 cases (33.3%), sinus tachycardia in 3 (8.3%), ischemic pattern in 1 (2.8%) and supraventricular tachycardia in 1 (2.8%). Echocardiographic exam was done in 29 patients (80.6%). Eighteen patients (62.1%) showed normal finding, 8 (27.6%) revealed concentric LV hypertrophy with normal LV systolic function, and 3 (10.3%) demonstrate LV systolic dysfunction (LV ejection fraction < 50%). Three showed transient LV dysfunction (2 with inverted Takotsubo-type cardiomyopathy and 1 with a diffuse hypokinesia pattern). Common presenting symptoms in the 3 cases were new onset chest discomfort and dyspnea which were not common in the other patients. Their echocardiographic abnormalities were normalized with conventional treatment within 3 days.

CONCLUSION: Out of total 36 patients with pheochromocytoma, 3 showed transient LV systolic dysfunction (catecholamine cardiomyopathy). Pheochromocytoma should be included as one of possible causes of transient LV systolic dysfunction.

KEY WORDS: Pheochromocytoma · Catecholamine cardiomyopathy · Echocardiography.

INTRODUCTION

Pheochromocytoma is a rare tumor derived from chromaffin cells of the adrenal gland. It can secrete excessive catecholamine and cause clinical problems.^{1,2)} Stimulation of alpha-adrenergic receptors results in elevated blood pressure, increased cardiac contractility, glycogenolysis, gluconeogenesis, and intestinal relaxation. Stimulation of beta-adrenergic receptors results in an increase in heart rate and contractility. Excessive catecholamine

release can cause transient reversible cardiomyopathy associated with pheochromocytoma.^{3,4)} There are many sporadic case reports about transient episode of heart failure associated with pheochromocytoma. However, there is no known article about the incidence of cardiomyopathy in the patients with pheochromocytoma. Thus we evaluated the patterns of clinical presentation and the incidence of catecholamine cardiomyopathy in Korean patients with pheochromocytoma.

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METHODS

From January 2004 to April 2011, all consecutive patients with pheochromocytoma were enrolled retrospectively. Pheochromocytoma was diagnosed by histologic examination after surgical removal. We investigated their clinical symptoms, serum catecholamine profiles, urinary excretion of catecholamines and radiologic findings including computerized tomography (CT) with review of their medical records.

The patterns of electrocardiography and echocardiography were also analyzed. The electrocardiographic examinations were performed at the time of diagnosis. Electrocardiograms were interpreted independently without knowledge of the clinical or echocardiographic finding by a specialist (J.H.K). Echocardiographic examinations were carried at the time of diagnosis and surgical removal. Complete two-dimensional, M-mode and Doppler studies were performed using standard parasternal, apical, and subcostal approaches using Vivid 7 (GE Medical Systems, Waukesha, Wisconsin). End-diastolic and end-systolic LV volumes were measured in the apical four and two chamber view with a modified Simpson's method. The LV ejection fraction was subsequently calculated. Mitral inflow velocities were calculated with a pulsed wave Doppler at the tip of the mitral valve. Mitral annular velocities were measured with tissue Doppler imaging of the mitral annulus. The calculated LV ejection fraction of less than 50% was considered the presence of LV systolic dysfunction. If there was a LV systolic dysfunction, a follow-up echocardiography examination was done, repeatedly.

Blood test for plasma catecholamines was done by a liquid chromatographic method (epinephrine less than 15 pg/mL, and norepinephrine less than 25 pg/mL are normal in our laboratory).⁵⁾ Urinary catecholamines were measured by a liquid chromatographic method and expressed as $\mu\text{g}/24$ hours (norepinephrine less than 80 $\mu\text{g}/24$ hours, epinephrine less than 22 $\mu\text{g}/24$ hours, vanillylmandelic acid less than 8 mg/24 hours, and metanephrine less than 0.8 mg/24 hours are normal in our laboratory).^{5,6)}

RESULTS

During the study period, total 36 patients (21 males, 49.8 \pm 15.8 years, range 14-81 years) with pheochromocytoma were enrolled. Their clinical characteristics were listed in Table 1. Most common presenting symptom was abdominal pain (36.1%). Nine (25.0%) of them had no clinical symptoms. Most common reason of detection of pheochromocytoma was routine screening (17, 47.2%). Others were evaluation of abdominal pain (8, 22.2%), dyspnea (4, 11.1%), hypertension (3, 8.3%), headache (3, 8.3%), and palpitation (1, 2.8%). Previous history of cardiovascular disease was rare. Cardiac risk factors were 47.2% with hypertension and 16.7% with diabetes. The serum glucose level was high (157.8 \pm 70.5 mg/dL).

All patients underwent electrocardiographic examination.

Table 1. Characteristics of the participants

Characteristic	n = 36
Male gender	21 (58.3%)
Age (year)	49.8 \pm 15.8 (14-81)
Hypertension	19 (52.8%)
Diabetes	6 (16.7%)
Initial symptoms	
Abdominal pain	13 (36.1%)
Headache	12 (33.3%)
Chest pain	6 (16.7%)
Palpitation	8 (22.2%)
Sweating	9 (25.0%)
Weight loss	7 (19.4%)
Flushing	2 (5.6%)
Dyspnea	2 (5.6%)
No symptom	9 (25.0%)
CT finding	
Location of mass	
Left adrenal gland	24 (66.7%)
Right adrenal gland	11 (30.6%)
Bilateral adrenal glands	1 (2.7%)
Maximal size (cm)	5.6 \pm 2.8
Cystic change	28 (77.8%)
Hemorrhage	27 (75.0%)
Serum glucose (mg/dL)	157.8 \pm 70.5 (80-321)
Blood catecholamines	
Epinephrine (pg/mL)	81.1 \pm 119.0 (0.04-321.8)
Norepinephrine (pg/mL)	286.7 \pm 446.2 (1.64-1439)
Urinary catecholamine excretion	
VMA (mg/d, < 8 mg/d)	19.6 \pm 22.2 (0.1-96.6)
Metanephrine (mg/d, < 0.8 mg/d)	1278.0 \pm 4059.1 (0.15-22107.4)
Epinephrine ($\mu\text{g}/\text{d}$, 1.7-22 $\mu\text{g}/\text{d}$)	155.0 \pm 334.0 (3.1-1530.6)
Norepinephrine ($\mu\text{g}/\text{d}$, 12.1-80 $\mu\text{g}/\text{d}$)	437.3 \pm 409.2 (11.9-1466.4)
Echocardiographic finding	
N/A	7 (19.4%)
Systolic function (n = 29)	
Normal	18 (62.1%)
LVH with normal systolic function	8 (27.6%)
LV systolic dysfunction	3 (10.3%)
Diastolic function (n = 29)	
Normal	7 (24.1%)
Relaxation abnormality	22 (75.9%)
Electrocardiographic finding	
Normal	19 (52.8%)
LVH	12 (33.3%)
Sinus tachycardia (> 100/min)	3 (8.3%)
Other findings	2 (5.6%)

CT: computerized tomography, VMA: vanillylmandelic acid, N/A: not assessed, LVH: left ventricular hypertrophy

Normal finding was the most common (19, 52.8%). LV hypertrophy was found in 12 (33.3%), sinus tachycardia (> 100/min) in 3 (8.3%) and other findings (2 nonspecific ST segment change and 1 supraventricular tachycardia) in 5.6%. Because there was no clinical symptoms and electrocardiographic abnormality, echocardiographic exam was not done in 7 patients. Of total 29 patients, most common finding was normal LV systolic function in 18 patients. Majority of patients (22, 75.9%) underwent echocardiographic examination showed relaxation abnormality.

Three patients showed transient LV systolic dysfunction (2 with inverted Takotsubo type cardiomyopathy and 1 with diffuse hypokinesia pattern). Common presenting symptoms were new onset chest discomfort and dyspnea. However, there was no relationship between the presence of LV systolic dysfunction with tumor size or presence of necrosis in it. Their electrocardiographic examinations demonstrated sinus tachycardia without evidence of ST segment change. All three patients admitted to the emergency department and cared in the intensive care unit. Their clinical profiles were summarized in the Table 2.

CASE 1

A 32-year-old man visited our emergency department with palpitation and squeezing chest pain. His initial blood pressure was 190/112 mmHg and electrocardiogram showed sinus tachycardia of 120/min. The initial electrocardiogram revealed slight ST-segment elevation in lead II, III, and aVF. Echocardiography demonstrated a midventricular dilatation of the LV

and decreased LV ejection fraction of 35% (Fig. 1A and B). However, the motion of the LV apex was preserved. Serum levels of cardiac biomarkers were increased. The serum level of N-terminal-pro-B type natriuretic peptide (NT-pro-BNP) was increased up to 733.3 pg/mL (normal range: < 200 pg/mL). The coronary arteries were free of any organic stenosis and LV angiogram showed severe hypokinesia in the mid to basal portion with preserved LV apical wall motion. The serum and 24-hour urine studies were compatible with pheochromocytoma. An abdominal CT showed an approximately 7.8 × 8.3 × 10.0 cm large septated cystic mass with irregular wall enhancement of the right adrenal gland and scintigraphy scan with ¹²³I-MIBG showed huge round uptake in the right adrenal gland. The patient was treated with oral furosemide, an oral alpha blocker and intravenous nitrate infusion. The low dose of beta blocker was initiated after alpha blockade. The follow up echocardiography after three days of treatment showed marked improvement of LV systolic function and decreased LV dimension. The LV ejection fraction was 59%, with no regional wall motion abnormalities (Fig. 1C and D).

CASE 2

A 41-year old man presented to the emergency room due to new-onset dyspnea. His initial blood pressure was 180/100 mmHg and heart rate was 140/min. The initial electrocardiogram demonstrated sinus tachycardia. Chest radiography showed pulmonary edema which improved after 3 days (Fig. 2). Serum levels of cardiac biomarkers were increased. NT-pro-BNP was markedly increased up to 34,489 pg/mL. Echocar-

Table 2. Clinical profiles of the patients with transient left ventricular dysfunction

	Case1	Case 2	Case 3
Gender / Age (year)	Male / 32	Male / 41	Female / 49
Initial symptoms	Palpitation, Chest discomfort		Dyspnea, Chest discomfort
Initial chest X-ray finding	Normal	Pul edema	Pul edema
Initial EchoCG finding	Inverted-Takotsubo cardiomyopathy	Inverted-Takotsubo cardiomyopathy	Global hypokinesia
Time to normalization of EchoCG finding	3 days	3 days	3 days
Blood catecholamine			
Epinephrine (pg/mL)	N/A	< 15	209.2
Norepinephrine (pg/mL)	N/A	< 25	299.8
Urinary catecholamine excretion			
VMA (mg/d)	31.9	41.7	25.6
Metanephrine (mg/d)	22107.4	11.2	7.2
Epinephrine (µg/d)	1530.6	422.2	604.1
Norepinephrine (µg/d)	1038.8	921.0	699.6
NT-Pro BNP (pg/ mL)	733.3	34489	2458
Cardiac enzymes			
CK (U/L)	138	3606	228
CK-MB (ng/mL)	3.84	109.3	20.5
Troponin-I (ng/mL)	1.74	21.56	6.3

EchoCG: echocardiography, VMA: vanillylmandelic acid, NT-Pro BNP: N-terminal Pro B-type natriuretic peptide, CK: creatinine kinase, Pul edema: pulmonary edema

diography showed severe LV dysfunction and a contractile abnormality, consisting of akinesis of the basal and mid ventricular segments and hyperkinesis of the apical segments (Fig. 3A and B). The patient was admitted at intensive care unit and intravenous administration of dobutamine, furosemide, and

digoxin. His symptoms were improved in one day despite of sporadic surge of blood pressure and pulse rate. The 24-hour urine study was compatible with pheochromocytoma. The abdominal CT revealed about $4.9 \times 5.7 \times 4.5$ cm sized right adrenal cystic mass with hemorrhage. Follow up echocardiogra-

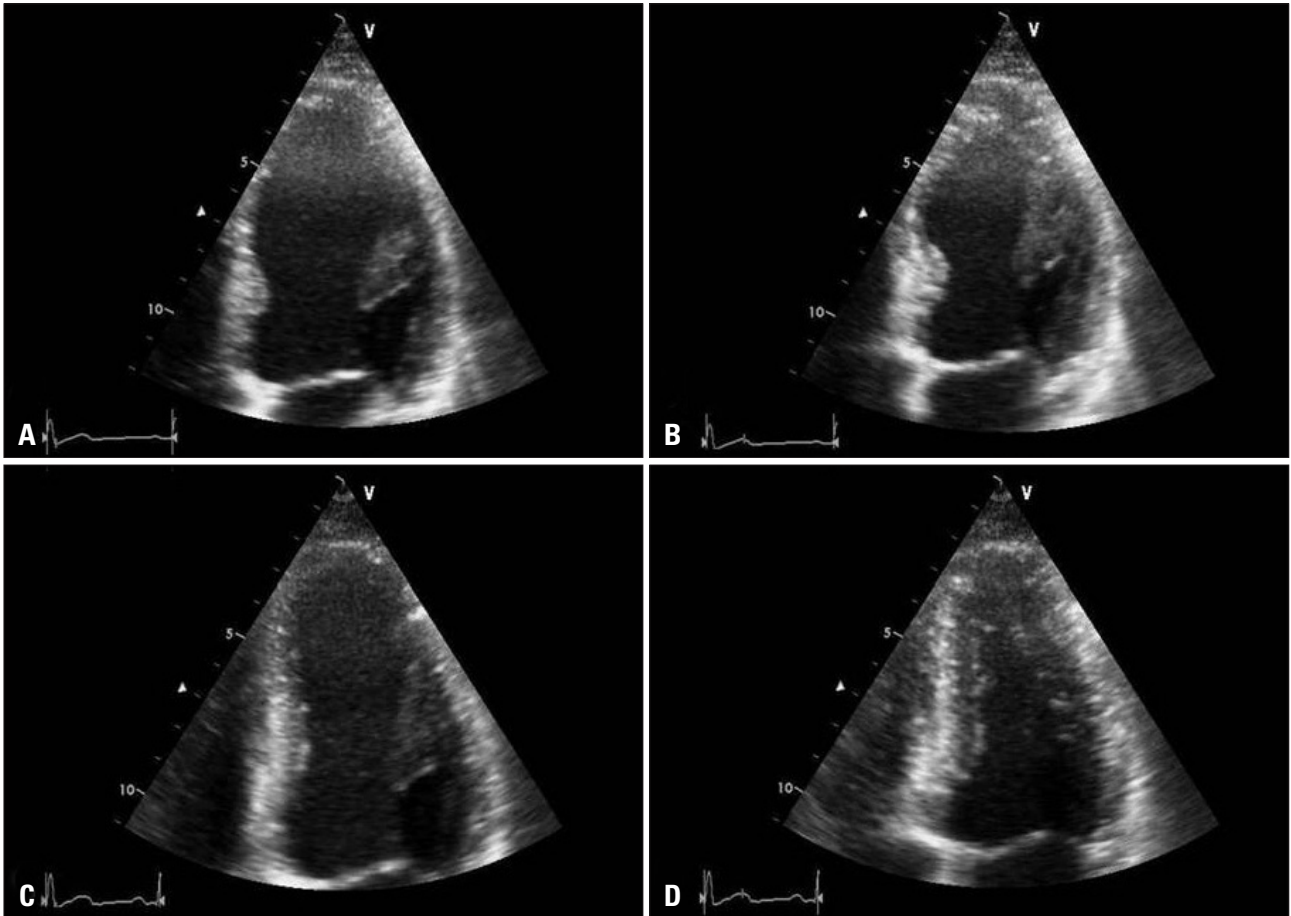


Fig. 1. An apical four-chamber view of the left ventricle in the emergency department is shown at end-diastole (A) and end-systole (B). At end-systole, mid- and basal ventricular ballooning was noted. The follow-up echocardiographic study was performed after three days of treatment. The left ventricular dimension was decreased and ballooning had disappeared (C at end-diastole and D at end-systole).

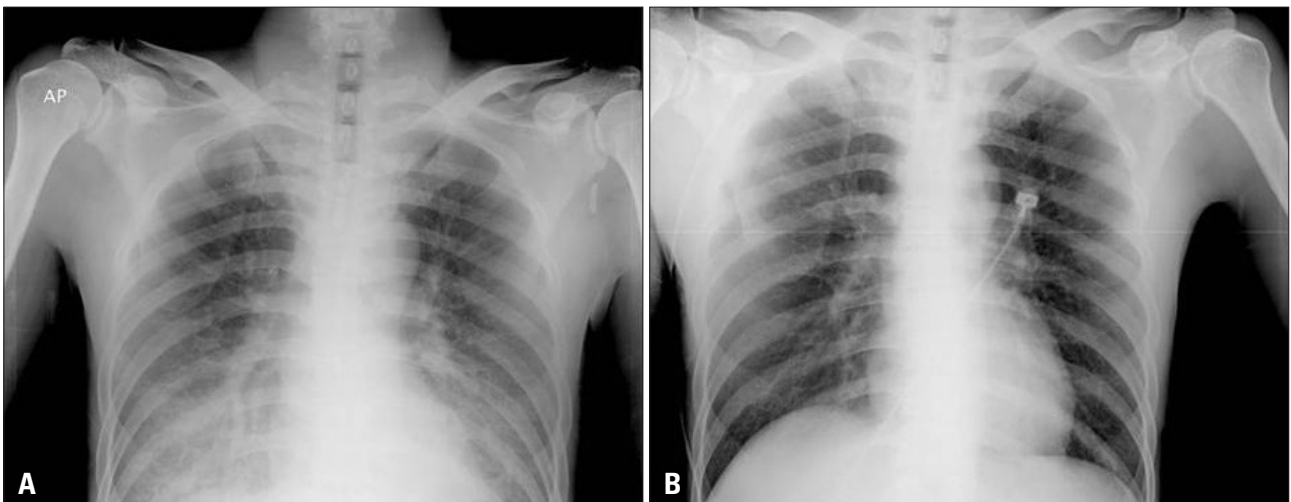


Fig. 2. Chest radiography shows pulmonary edema which improved after 3 days of treatment. A: On admission. B: After treatment.

phy, repeated after two days, demonstrated normalized LV systolic function and regional wall motion abnormalities (Fig. 3C and D). The elective laparoscopic right adrenalectomy was performed after 4 weeks of therapy including alpha and beta blockers.

CASE 3

A 49-year-old woman with hypertension and diabetes mellitus was admitted to emergency room with dyspnea and chest discomfort. She complained palpitation and recurrent headache for several months. Her initial blood pressure was 160/114

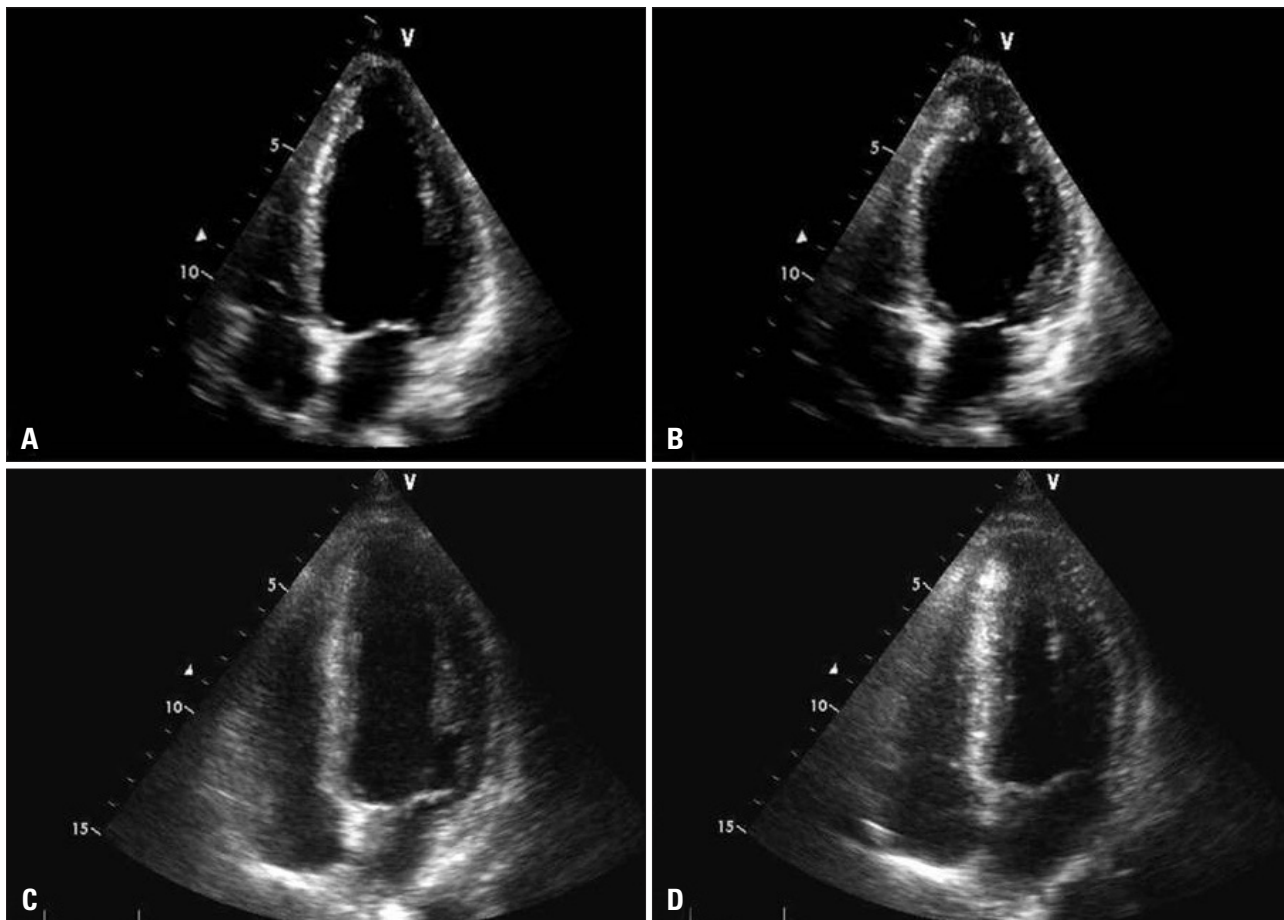


Fig. 3. An apical four-chamber view of the left ventricle in the emergency department is shown at end-diastole (A) and end-systole (B). Apical wall motion is normal. However, mid- and basal ventricular ballooning is noted. The follow-up echocardiographic study performed after three days of treatment demonstrates decreased left ventricular size and disappeared mid- and basal ventricular ballooning (C at end-diastole and D at end-systole).

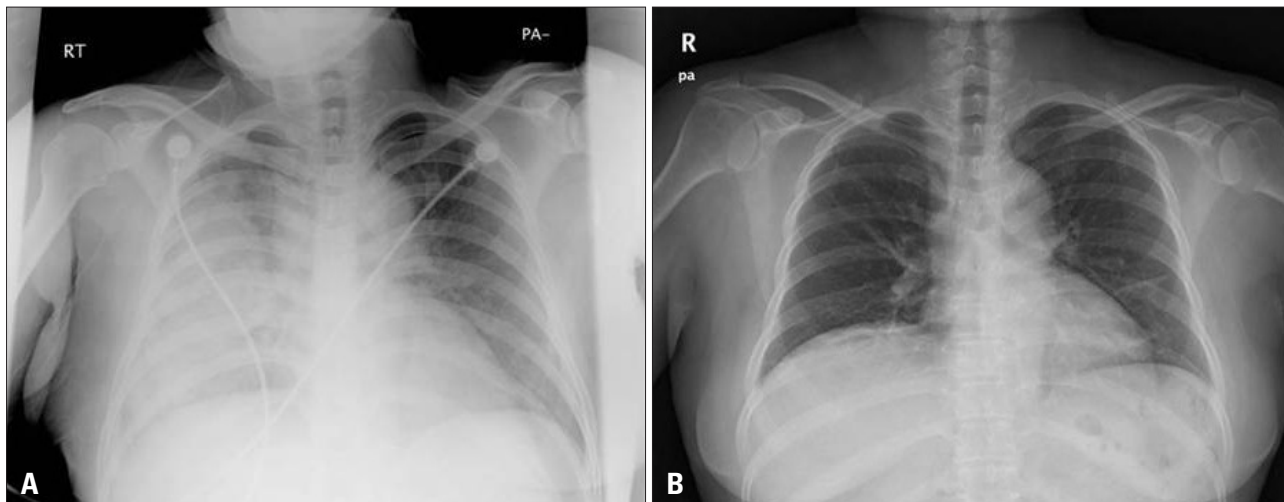


Fig. 4. Chest radiography demonstrates marked pulmonary edema which normalized after 3 days of treatment. A: On admission. B: After treatment.

mmHg and heart rate was 100/min. The initial electrocardiogram demonstrated sinus tachycardia. Chest radiography showed marked pulmonary edema (Fig. 4). Because the patient showed severe hypoxemia, she was intubated and cared with ventilator in the intensive care unit. Her condition improved dramatically after 1 day and ventilator was removed after 2 days. Cardiac enzymes were slightly elevated and NT-pro-BNP increased up to 2,458 pg/mL. Echocardiography showed severe LV systolic dysfunction with an estimated ejection fraction of 20% and severe hypokinesia of all segments. A 24-hour urinary catecholamine excretion was compatible with pheochromocytoma. Follow up echocardiography, repeated after two days, demonstrated normalized LV systolic function and regional wall motion abnormalities. Cardiac catheterization was performed and angiographically normal epicardial coronary arteries. The patient was hemodynamically stabilized with conventional treatment. The abdominal CT scan revealed about 3.3 × 6.2 sized tumor of the left adrenal gland and 131I-MIBG scintigraphy showed a hot-uptake lesion of the same location.

DISCUSSION

The prevalence of catecholamine cardiomyopathy associated with pheochromocytoma is about 10% (3 of 29 patients) in our study. The patterns of cardiac involvement are 2 inverted-Takotsubo cardiomyopathies and 1 diffuse severe hypokinesia. All three patients showed complete recovery with inotropic support and conventional treatment within 3 days.

Pheochromocytomas are rare catecholamine producing tumors typically located in the adrenal gland or along the sympathetic ganglia. Due to secretion of catecholamines, they usually present with a classic triad of headache, tachycardia and sweating.⁷⁾

Shub et al.⁸⁾ reported echocardiographic patterns in 26 patients with pheochromocytoma. In their data, most common echocardiographic finding was normal or increased systolic function (80% of the patients). The result of our study is consistent with this study. However, relaxation abnormality is the most common finding in our study (22, 75.8%). The increased incidence of diastolic dysfunction may be associated with injury of myocytes or increased oxidative stress by circulating catecholamines.⁹⁾¹⁰⁾

It has also been reported to cause cardiac manifestations including a transient, reversible cardiomyopathy (catecholamine cardiomyopathy).¹¹⁾ Shaw et al.¹¹⁾ firstly reported echocardiographic feature of catecholamine cardiomyopathy associated with pheochromocytoma in the late 1980s. It resembles Takotsubo cardiomyopathy (transient apical ballooning syndrome) presenting with hyperkinesis of the basal segments and apical hypokinesia.³⁾¹²⁻¹⁴⁾ The LV systolic dysfunction usually recovers completely within several days. Proposed potential mechanisms of transient LV ballooning include micro-vascular dysfunction of the coronary arteries, multivessel epicardial spasm, impaired fatty acid metabolism, myocarditis and catechol-

amine-mediated myocardial dysfunction.¹⁵⁾¹⁶⁾ Although the mechanism of the association between sympathetic stimulation and myocardial stunning is still unknown, several proposed mechanisms have been proposed including coronary arterial spasm¹⁷⁾ and direct injury to myocytes.⁹⁾ The apex is more vulnerable to a sudden increase in circulating catecholamine levels may be due to different distribution of sympathetic nerves¹⁸⁾ and dissimilar density of sympathetic nerves in the heart.¹⁹⁾ More recently, a variant of Takotsubo cardiomyopathy, the 'inverted-Takotsubo cardiomyopathy' has been described.¹⁵⁾ It distinguished by dysfunction of the basal and mid-ventricular segments with preserved function of the apical segments. Cases of inverted-Takotsubo cardiomyopathy associated with pheochromocytoma were also reported.²⁰⁻²²⁾ Two of our cases showed inverted-Takotsubo cardiomyopathy which recovered completely within 3 days. The variations in segmental involvement regardless of coronary anatomy in patients with excessive catecholamine levels may suggest different susceptibility to sympathetic stimulation from individual to individual.²⁰⁾

Despite this study firstly described the prevalence of transient LV systolic dysfunction with echocardiographic examination, this study has many limitations. First, this study is a retrospective study with review of their medical records. The incidence and pattern of LV systolic dysfunction could not be assessed exactly. However, all three patients with LV systolic dysfunction complained new onset dyspnea and chest discomfort led to visiting emergent department. Their serum NT-Pro BNP levels were elevated and echocardiographic examination revealed the presence of LV systolic dysfunction. Moreover, 9 of total patients had no presenting symptoms suggesting presence of LV systolic dysfunction. Second, echocardiographic examination was not performed in all participants. Echocardiographic examination was not performed in the patients without clinical symptoms and with normal electrocardiographic findings (7, 19.4%). Pheochromocytoma is a very rare tumor and the detection is difficult especially without presenting symptoms. To evaluate the exact incidence and pattern of catecholamine cardiomyopathy associated with pheochromocytoma, prospective study will be needed.

In conclusion, of total 36 patients with pheochromocytoma, 3 showed transient LV systolic dysfunction (catecholamine cardiomyopathy associated with pheochromocytoma). Two of their echocardiographic patterns were inverted-Takotsubo cardiomyopathy and 1 was diffuse LV hypokinesia. Their echocardiographic abnormalities were normalized with conventional treatment within 3 days.

REFERENCES

1. Sheps SG, Jiang NS, Klee GG, van Heerden JA. *Recent developments in the diagnosis and treatment of pheochromocytoma.* *Mayo Clin Proc* 1990;65:88-95.
2. Bravo EL, Gifford RW Jr. *Current concepts. Pheochromocytoma: diagno-*

- sis, localization and management. *N Engl J Med* 1984;311:1298-303.
3. Wood R, Commerford PJ, Rose AG, Tooke A. Reversible catecholamine-induced cardiomyopathy. *Am Heart J* 1991;121:610-3.
 4. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation* 2008;118:397-409.
 5. Gerlo EA, Sevens C. Urinary and plasma catecholamines and urinary catecholamine metabolites in pheochromocytoma: diagnostic value in 19 cases. *Clin Chem* 1994;40:250-6.
 6. Moyer TP, Jiang NS, Tyce GM, Sheps SG. Analysis for urinary catecholamines by liquid chromatography with amperometric detection: methodology and clinical interpretation of results. *Clin Chem* 1979;25:256-63.
 7. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. *Medicine (Baltimore)* 1991;70:46-66.
 8. Shub C, Cueto-Garcia L, Sheps SG, Ilstrup DM, Tajik AJ. Echocardiographic findings in pheochromocytoma. *Am J Cardiol* 1986;57:971-5.
 9. Bolli R, Marbán E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev* 1999;79:609-34.
 10. Yamanaka O, Yasumasa F, Nakamura T, Ohno A, Endo Y, Yoshimi K, Miura K, Yamaguchi H. "Myocardial stunning"-like phenomenon during a crisis of pheochromocytoma. *Jpn Circ J* 1994;58:737-42.
 11. Shaw TR, Rafferty P, Tait GW. Transient shock and myocardial impairment caused by pheochromocytoma crisis. *Br Heart J* 1987;57:194-8.
 12. Schuiki ER, Jenni R, Amann FW, Ziegler WH. A reversible form of apical left ventricular hypertrophy associated with pheochromocytoma. *J Am Soc Echocardiogr* 1993;6:327-31.
 13. Takizawa M, Kobayakawa N, Uozumi H, Yonemura S, Kodama T, Fukusima K, Takeuchi H, Kaneko Y, Kaneko T, Fujita K, Honma Y, Aoyagi T. A case of transient left ventricular ballooning with pheochromocytoma, supporting pathogenetic role of catecholamines in stress-induced cardiomyopathy or takotsubo cardiomyopathy. *Int J Cardiol* 2007;114:e15-7.
 14. Lassnig E, Weber T, Auer J, Nömeier R, Eber B. Pheochromocytoma crisis presenting with shock and tako-tsubo-like cardiomyopathy. *Int J Cardiol* 2009;134:e138-40.
 15. Hurst RT, Askew JW, Reuss CS, Lee RW, Sweeney JP, Fortuin FD, Oh JK, Tajik AJ. Transient midventricular ballooning syndrome: a new variant. *J Am Coll Cardiol* 2006;48:579-83.
 16. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, Yoshiyama M, Miyazaki S, Haze K, Ogawa H, Honda T, Hase M, Kai R, Morii I; Angina Pectoris-Myocardial Infarction Investigations in Japan. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. *J Am Coll Cardiol* 2001;38:11-8.
 17. Lacy CR, Contrada RJ, Robbins ML, Tannenbaum AK, Moreyra AE, Chelton S, Kostis JB. Coronary vasoconstriction induced by mental stress (simulated public speaking). *Am J Cardiol* 1995;75:503-5.
 18. Pierpont GL, DeMaster EG, Cohn JN. Regional differences in adrenergic function within the left ventricle. *Am J Physiol* 1984;246:H824-9.
 19. Kawano H, Okada R, Yano K. Histological study on the distribution of autonomic nerves in the human heart. *Heart Vessels* 2003;18:32-9.
 20. Kim EM, Park JH, Park YS, Lee JH, Choi SW, Jeong JO, Seong IW. Catecholamines may play an important role in the pathogenesis of transient mid- and basal ventricular ballooning syndrome. *J Korean Med Sci* 2008;23:898-902.
 21. Kim S, Yu A, Filippone LA, Kolansky DM, Raina A. Inverted-Takotsubo pattern cardiomyopathy secondary to pheochromocytoma: a clinical case and literature review. *Clin Cardiol* 2010;33:200-5.
 22. Kim TS, Chu EH, Kang HH, Chun SW, Cho EJ, Kim JH. A case of reversal of takotsubo cardiomyopathy in patient with pheochromocytoma. *J Cardiovasc Ultrasound* 2007;15:50-4.