

## Retrospective Study

## Pheochromocytoma and stress cardiomyopathy: Insight into pathogenesis

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### Abstract

#### AIM

To investigate the occurrence of cardiomyopathy (CMP) in a cohort of patients with histologically proven pheochromocytoma (pheo), and to determine if catecholamine excess was causative of the left ventricular (LV) dysfunction.

#### METHODS

A retrospective chart review spanning years 1998 through 2014 was undertaken and patients with a diagnosis of pheo confirmed with histopathologic examination were included. Presenting electrocardiograms and cardiac imaging studies were reviewed. Transthoracic echocardiography (TTE), ventriculography or single positron emission computed tomography imaging was evaluated and if significant abnormalities [left ventricular hypertrophy (LVH) or LV dysfunction] were noted in the pre operative period a follow up post-operative study was also analyzed. Multivariate analysis using logistic regression was used to investigate independent predictors for outcomes of interest, LV dysfunction and LVH.

#### RESULTS

We identified 18 patients with diagnosis of pheo confirmed on pathology. Mean age was  $54.3 \pm 19.3$  years and 11 (61.1%) patients were females. 50% of such patients had either resistant hypertension or labile blood pressures during hospitalization, which had raised suspicion for a pheo. Cardiac imaging studies were available for 12 (66.7%) patients at the time of inclusion into study and preceding the adrenalectomy.

7 (58.3%) patients with a TTE available for review had mild or more severe LVH while 3 (25%) patients had LV dysfunction of presumably acute onset. In a multivariate analysis, elevated catecholamine levels as assessed by urinary excretion of metabolites was not an independent predictor of development of LV systolic dysfunction or of presence of LVH on TTE. Two female patients with a preceding history of hypertension had marked LV hypertrophy and systolic anterior motion of the mitral valve. Prolongation of the QTc interval was noted in 5 (27.8%) patients but no acute arrhythmias were observed in any patient.

### CONCLUSION

This study adds to the growing body of literature on the predilection of patients with pheochromocytomas to develop non-ischemic CMP. Degree of catecholamine excess as measured by urinary secretion of metabolites did not predict the development of CMP but 2 of 3 patients developed CMP in the setting of significant acute physiologic stress. Our findings provide support to the proposed etiologic role of elevated catecholamines in TC and other stress induced forms of CMP, however, activation of a brain-neural-cardiac axis from acute stress and local release of catecholamines but not chronic catecholamine elevations are likely to be responsible in pheo related CMP.

**Key words:** Pheochromocytoma; Cardiomyopathy; Stress

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**Core tip:** A non-ischemic cardiomyopathy (CMP) may be observed in patients with pheochromocytoma and shares several features with takotsubo cardiomyopathy. Although it is believed that pheochromocytoma related CMP is due to the catecholamine excess, the exact pathogenesis is unclear. CMP in pheochromocytoma patients often follows acute stress and while clinical course maybe complicated by acute hemodynamic compromise, prognosis is good. On the basis of our findings, where 3 of 18 pheochromocytoma patients developed an acute CMP, we suggest that activation of a brain-neural-cardiac axis from acute stress and local release of catecholamines but not chronic catecholamine elevations may likely be responsible for pheo related CMP.

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### INTRODUCTION

Pheochromocytomas (pheo) are rare tumors of chrom-

affin cells originating most frequently in the adrenal medulla<sup>[1]</sup>. Catecholamines are secreted by these tumors in varying amounts and proportions<sup>[1]</sup> accounting for the various associated clinical symptoms. Cardiovascular manifestations of this catecholamine excess are several. Hypertension (both sustained and paroxysmal), ventricular hypertrophy, myocardial infarction, and arrhythmias (supraventricular and ventricular) are reported to occur in relation to this hormonal excess<sup>[2]</sup>. Left ventricular (LV) dysfunction may develop in patients with pheo and is termed catecholamine cardiomyopathy (CC)<sup>[2]</sup>. Although thought to arise from the incident catecholamine excess, the exact mechanism of such cardiac dysfunction remains elusive<sup>[3]</sup>. "Stress" or takotsubo cardiomyopathy (TC) is a syndrome characterized by transient acute LV systolic dysfunction encompassing multiple vascular territories in the absence of flow-limiting epicardial coronary artery disease (CAD)<sup>[4,5]</sup> and is purported to be caused by myocardial stunning resulting from exaggerated adrenergic signaling<sup>[6]</sup>. A similar morphologic pattern of LV dysfunction characterized by apical akinesis with preservation of contractility of more basal LV segments and described classically as apical ballooning has been described for both TC and CC<sup>[3,7]</sup>. It is therefore plausible that a common etiologic link exists between these two entities. We sought to investigate the occurrence of cardiomyopathy (CMP) in a cohort of patients with histologically proven pheo and to determine if catecholamine excess was causative of this LV dysfunction.

### MATERIALS AND METHODS

#### Patient characteristics

A retrospective chart review spanning years 1998 through 2014 was undertaken to search for patients with a diagnosis of pheo. Medical records of patients with a probable diagnosis of pheo were perused and patients were included in this study only if such diagnosis had been confirmed with histopathologic examination. The institutional review board approved the study protocol. Data on patient demographics, clinical characteristics, radiologic imaging, laboratory investigations (specifically plasma and urine catecholamine levels); and surgical and pathologic findings were collected. Presenting electrocardiograms (ECG) and cardiac imaging study results were reviewed. Transthoracic echocardiography (TTE), ventriculography and single positron emission computed tomography (SPECT) imaging was evaluated and if significant abnormalities [LV hypertrophy (LVH) or LV dysfunction] were noted in the pre-operative period a follow up post-operative study was also analyzed if available. Two physicians unaware of the knowledge of the diagnoses independently interpreted the ECG and imaging studies. LVH on ECG was diagnosed if any of the accepted voltage criteria was judged to be satisfied<sup>[8]</sup>. Echocardiograms were obtained according to a standardized institutional protocol [parasternal, apical, subcostal and suprasternal imaging planes were

Table 1 Patient demographics

	<i>n</i> = 18
Age (yr)	54.33 ± 19.30
Female gender ( <i>n</i> , %)	11 (61.1)
Hypertension ( <i>n</i> , %)	12 (66.7)
Acute hypertension ( <i>n</i> , %)	6 (33.3)
DM ( <i>n</i> , %)	5 (27.8)
HLD ( <i>n</i> , %)	4 (22.2)
CAD ( <i>n</i> , %)	1 (5.6)
Migraine ( <i>n</i> , %)	2 (11.1)

DM: Diabetes mellitus; HLD: Hyperlipidemia; CAD: Coronary artery disease.

scanned using Vivid 7 machine (GE® medical systems, Waukesha, Wisconsin, United States)]. Two dimensional (2D), M-mode and Doppler modalities were utilized. LVEF was calculated using the Simpson's method of disc summation and adjudicated independently by two reviewers. Our primary outcome of interest was the incidence of LV dysfunction, which was defined as an LVEF ≤ 50%, with or without regional wall motion abnormalities. LVH was defined as an increase in LV mass indexed for body surface area per guideline recommendations of the American Society of Echocardiography<sup>[9]</sup>. Disagreements in ECG or TTE interpretation were resolved by a consensus meeting or after consultation with a third author. Plasma and urine catecholamine levels were measured by a method of liquid chromatography according to current diagnostic guidelines<sup>[10]</sup>.

### Statistical analysis

Results are expressed as numbers (frequencies) for categorical variables and mean ± standard deviation (SD) for continuous variables. Differences between groups were analyzed with the use of the Student's *t* test for continuous variables and the chi-square test for categorical variables respectively. Multivariate logistic regression analysis was used to investigate predictors for outcomes of interest. A two sided *P*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS, Statistics version 20.0 (IBM Corp., Armonk, New York).

## RESULTS

We identified 18 patients with pathologically confirmed pheo. The demographics, clinical presentations and comorbidities for these patients are described in Table 1. Mean age was 54.3 ± 19.3 years (range 17-83 years) and 11 (61.1%) patients were females; 9 (50%) tumors were localized to the left adrenal gland while 5 (27.8%) tumors were bilateral, extra-adrenal or metastatic (Table 2). Two (11.1%) patients presented with a recurrence and both had metastatic disease. One patient, a young male had an extra-adrenal paraganglioma in close proximity to the urinary bladder. All except for one patient who had diffuse metastatic disease

Table 2 Tumor characteristics

	<i>n</i> (%)
Left	9 (50)
Right	4 (22.2)
Bilateral	1 (5.6)
Extra-adrenal	2 (11.1)
Metastatic	2 (11.1)
Size (range) (c.c.)	15.63-3025
Incidental diagnosis	14 (77.8)
Open adrenalectomy	9/17 (52.9)

underwent surgical removal of pheo. Open (52.9%) and laparoscopic approaches were utilized for tumor removal. A history of hypertension was present in 12/18 (66.7%) patients of which 50% was either resistant or labile. Prior history of CAD was uncommon; one patient had known history of obstructive CAD and another was found to have non-flow limiting atherosclerosis. Two patients were admitted for acute cardiovascular events. The first was a 37-year-old woman with a large ischemic stroke in the middle cerebral artery territory. She had experienced a self-resolving episode of LV dysfunction presumed to be secondary to a viral myocarditis 5 years before this event. Bilateral adrenal cystic tumors were found on CT and she subsequently underwent successful bilateral adrenalectomy. No LV dysfunction was noted during this time or subsequently. The other patient was a 77-year-old woman who was admitted originally with complaint of chest pain accompanied by headache and nausea suspicious for an acute coronary syndrome. Coronary angiography was negative and systolic blood pressure (BP) elevation of more than 200 mmHg had initiated a search for pheo. Overall, 14 (77.8%) patients had incidentally noted adrenal masses. One of these patients had an existing diagnosis of multiple endocrine neoplasia syndrome type 2b and was undergoing serial biochemical testing to rule out hormonal production for a known history of an enlarging adrenal mass. Plasma catecholamine secretion and 24-h urine catecholamine excretion were elevated to varying degrees in most patients (Tables 3 and 4). All patients survived to discharge after adrenalectomy.

LV function was evaluated in 12 (66.7%) patients at the time of inclusion into study and preceding the adrenalectomy (Table 5) and, thus, no assessment of LVEF was available for 6 patients and these patients were excluded from statistical comparisons. Seven (58.3%) patients with a TTE available for review had mild or more severe LVH while 3 (25%) patients had LV dysfunction of presumably acute onset. LVH and LV dysfunction patients were serially compared with patients without these findings serving as controls. Clinical characteristics, catecholamine secretion, TTE and ECG findings were compared using multivariate analysis, and elevated catecholamine levels as assessed by urinary excretion of metabolites was not found to be an independent predictor of development of LV systolic dysfunction or of presence of LVH on TTE.

Two of the 3 patients with LV dysfunction had global

**Table 3 Plasma catecholamine secretion**

(n) (lab normal, pg/mL)	Mean ± SD (pg/mL)
Epi (7/18) (< 99)	873.86 ± 2074.92
NE (7/18) (< 339)	4121.43 ± 4833.55
NM (10/18) (< 111)	1506.1 ± 1856.72
Meta (9/18) (< 60)	1065.33 ± 1668.24

Epi: Epinephrine; NE: Norepinephrine; NM: Normetanephrine; Meta: Metanephrine.

**Table 4 Urine catecholamine excretion**

(n) (lab normal, ug/24 h)	Mean ± SD (ug/ 24 h)
NE (11/18) (< 140)	1099.27 ± 1233.70
Epi (11/18) (< 24)	307.73 ± 520.34
Dopa (11/18) (< 610)	377.91 ± 239.94
NM (9/18) (< 1050)	12960.67 ± 15197.26
Meta (10/18) (< 640)	22030.4 ± 40060.17
VM (6/18) (< 6.7 mg/dL)	3498.17 ± 8380.88

Epi: Epinephrine; NE: Norepinephrine; NM: Normetanephrine; Meta: Metanephrine; Dopa: Dopamine; VM: Vanillylmandelic acid.

hypokinesia. The first patient was an apparently healthy 47-year-old male who had a precipitous decline in BP after an initial malignant elevation shortly after elective endotracheal intubation and induction of anesthesia. Acute ST-segment elevation was noted on an ECG and warranted an emergent coronary angiography. No significant CAD or spasm was reported but severe diffuse hypokinesia was observed on TTE. Peak cardiac troponin I level was 6.8 ng/mL. Elevated 24-h urine catecholamine levels prompted a CT scan at which time a large left adrenal tumor was identified and subsequently excised. The second patient was a 64-year-old man who was admitted for severe anaphylactic reaction following multiple Hymenoptera stings. Clinical course was complicated by acute pulmonary edema and BP was labile. Acute severe diffuse LV hypokinesia and elevated cardiac troponins suggested an acute coronary syndrome, which was subsequently ruled out with a normal coronary angiogram. Pheo was detected and the tumor was excised. A follow up TTE (10 d) showed resolution of LV dysfunction and mild LVH. The third patient was a 67-year-old woman who was undergoing evaluation for severe systemic hypertension. No obstructive CAD was found on coronary angiography done previously when she was noted to have an abnormal ECG in the setting of dyspnea and chest pressure. A diagnosis of "classic" TC was made at that time in view of mid to distal wall segment hypokinesia consistent with "apical ballooning". An adrenal mass and elevated catecholamine levels were noted on a second presentation and a right adrenalectomy was performed for a moderate sized pheo.

Two women with preceding history of hypertension had marked LV hypertrophy. One such patient with septal and posterior wall thickness of 18 mm had systolic anterior motion of the mitral valve but no

**Table 5 Echo and electrocardiograms findings of study cohort**

	n (%)
Echo available	12
LV dysfunction	3/12 (25)
LVEF (%) (mean ± SD)	50 ± 16.88
Prior LV dysfunction	1/12 (8.3)
Asymmetric hypertrophy with mitral SAM	2/12 (16.67)
LVH	7/12 (58.3)
LVH on ECG	2/18 (11.1)
Prolonged QTc	5/18 (27.78)

QTc prolongation defined as > 440 ms in males; > 460 ms in females. LV: Left ventricle; LVH: Left ventricle hypertrophy; LVEF: LV ejection fraction; SAM: Systolic anterior motion; ECG: Electrocardiogram.

resting gradient across the LV outflow tract (LVOT). The LVH resolved post adrenalectomy in this patient. The second patient had asymmetric septal hypertrophy and a resting LVOT gradient of 23 mmHg. LVH was present on admission ECG in 11.1% patients, which resolved after tumor removal in 1 patient. Prolongation of the QTc interval (> 440 ms in males and > 460 ms in females) was noted in 5 (27.8%) patients. A univariate analysis for predictors of QTc prolongation was attempted, three of those patients were females, 4 had LVH by echo criteria and 2 had acute LV dysfunction. No acute arrhythmias were observed in any patient.

## DISCUSSION

In our study, 3 out of 18 patients with histologically proven pheochromocytoma were found to have de novo non-ischemic CMP which was defined as acute onset of systolic dysfunction with LVEF ≤ 50% in the absence of flow limiting CAD on coronary angiogram. The prevalence of this "idiopathic" pheo-related CMP was therefore 17% in the overall cohort, and 25% for patients who underwent any imaging for assessment of LV function. Previous studies have reported that the incidence of such pheo-related CMP is approximately 11%<sup>[11,12]</sup>. Overall, 7.5% of patients with TC have been found to have a pheo subsequently<sup>[13]</sup> and therefore it is recommend that pheo be excluded in patients with TC<sup>[14]</sup>. Elevation of circulating catecholamine levels in TC<sup>[6]</sup> and with pheo suggests excess catecholaminergic activity may be a shared pathogenic mechanism. Catecholamines cause myocardial toxicity by enhancing lipid mobility, calcium overloading, oxygen derived free radical production, increased sarcolemmal permeability as well as by provoking a state of oxygen supply-demand mismatch<sup>[15]</sup>. Further, recurrence of CMP in patients with unresected pheo<sup>[3]</sup> and resolution of CMP after treatment of adrenergic excess also suggest a causal relationship between catecholamine excess from pheo and CMP.

Provocation of a brain-heart-neural axis by various emotional and physical "stressors" has been theorized to result in massive releases of catecholamines locally into cardiac tissue while only a small leak occurs into

the systemic circulation<sup>[16,17]</sup>. In 2 of 3 patients that developed acute LV dysfunction in our study such events followed acute stress, suggesting that increases in catecholamine levels over and above the background elevation precipitated by “stress” may provoke acute LV dysfunction in pheo patients in a manner similar to TC. No independent predictors of LV dysfunction were found in this study including degree of adrenergic excess as assessed by urinary catecholamine excretion. In a study of 5 patients with TC like LV dysfunction, catecholamines levels were elevated in coronary sinus but not peripheral blood suggesting local norepinephrine release<sup>[18]</sup>. Endogenous release of catecholamines from myocardial sympathetic nerve terminals rather than circulating catecholamines may therefore mediate neurocardiogenic injury explaining the noted lack of higher catecholamine levels in pheo patients with acute LV dysfunction despite an attendant “acute stress”<sup>[19]</sup>. The absence of universal LV dysfunction despite the chronic adrenergic excess in all pheo patients is also intriguing. Persistent elevation of plasma catecholamine levels might induce adrenergic receptor desensitization *via* mechanisms that include receptor modulation and uncoupling from down-stream effectors<sup>[20,21]</sup>. Genetic susceptibility mediated through adrenergic receptor<sup>[22,23]</sup> and G protein coupled receptor kinase polymorphisms (GRK5)<sup>[24]</sup> may also account for differences in predisposition to cardiac dysfunction in pheo and TC related LV dysfunction despite similar catecholamine elevations.

Despite sharing a common morphology and possibly a shared etiology, pheo related CMP tends to differ from “idiopathic” TC in terms of patient demographics and clinical features. A study based on a population of 38 cases assimilated from published case reports of pheo related TC found such patients to be younger; and although the majority was still females, the sexual inequality was less skewed compared to TC patients without pheo<sup>[3]</sup>. Such patients experienced an inciting event less often but experienced more recurrent episodes (13.2% vs 3.5%).

Our study has some limitations. First, the sample size is small. However, this is related to the rare incidence of the disease process being studied. Second is the utilization of a retrospective design, again necessitated by the infrequent occurrence of the disease.

In conclusion, this study adds to the growing body of literature on the predilection of patients with pheo to develop non-ischemic CMP. In doing so it provides support for the proposed etiologic role of elevated catecholamines in TC and other stress induced forms of CMP. Degree of catecholamine excess as measured by urinary secretion of metabolites did not predict the development of CMP but 2 of 3 patients developed CMP in the setting of significant acute physiologic stress. Thereby acute stress mediated activation of a brain-neural-cardiac axis and local release of catecholamines as has been described previously but not chronic catecholamine elevations are likely to be responsible in pheo related CMP.

## COMMENTS

### Background

Pheochromocytomas are adrenal medullary tumors associated with a chronic elevation in catecholamine levels. They can rarely be associated with a non-ischemic cardiomyopathy.

### Research frontiers

Acute cardiomyopathy which may develop in patients with a pheochromocytoma is similar to “stress” or “takotsubo” cardiomyopathy in several ways including an elevated levels of catecholamines in both conditions. This suggests that the two forms of cardiac dysfunction might share a common etiologic link.

### Innovations and breakthroughs

Pheochromocytoma related cardiomyopathy developed in 3 of 18 patients. Two of these patients experienced an acute stressful event in a manner similar to classic takotsubo cardiomyopathy. The authors did not find an association between urinary excretion of catecholamines and development of cardiac dysfunction.

### Applications

The findings of this study need to be confirmed in a larger multicenter international registry.

### Terminology

Pheochromocytoma: Adrenal medulla tumors that may secrete varying amounts and combinations of catecholamines; Takotsubo cardiomyopathy: A form of acute cardiac dysfunction that develops classically after an acute stressful events and without obstruction of epicardial coronary arteries.

### Peer-review

This paper is interesting review concerning association pheochromocytoma and cardiomyopathy. Therefore, this article should be published.

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