Inverted-Takotsubo Pattern Cardiomyopathy Secondary to Pheochromocytoma: A Clinical Case and Literature Review

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ABSTRACT

Takotsubo cardiomyopathy is an increasingly recognized clinical syndrome of transient left ventricular dysfunction, commonly with apical ballooning, in the context of physical or emotional stress. Recently, an inverted-Takotsubo contractile pattern has been described with hypokinesis of the basal and mid-ventricular segments and sparing of the apex. We report a case of a 30-year-old man presenting with transient left ventricular dysfunction in an inverted-Takotsubo contractile pattern, associated with a newly discovered pheochromocytoma, and present a literature review of the inverted-Takotsubo contractile pattern cardiomyopathy.

Introduction

Pheochromocytomas are rare catecholamine-secreting tumors typically located in the adrenal medulla or along the sympathetic ganglia. Although they usually present with a classic triad of headache, sweating, and tachycardia,[1] pheochromocytomas have also been reported to cause cardiac symptomology including a transient, reversible cardiomyopathy.[2,3] Coincident with the increasingly widespread utilization of cardiac imaging, specific patterns of wall motion abnormalities seen in pheochromocytoma-induced cardiomyopathy have been identified and have been found to be very similar to those seen in Takotsubo cardiomyopathy.[4–7]

Also known as stress-induced cardiomyopathy or apical ballooning syndrome, Takotsubo cardiomyopathy is an increasingly recognized clinical syndrome classically characterized by the rapid development and subsequent resolution of severe, reversible left ventricular dysfunction involving the mid-ventricular and apical segments, which cannot be attributed to obstructive coronary artery disease.[8] Takotsubo cardiomyopathy is usually triggered by emotional or physical stress and can appear identical to myocardial infarction with elevated cardiac biomarkers and electrocardiographic changes. More recently, a variant of this syndrome, the "inverted-Takotsubo" pattern, distinguished by dysfunction of the basal and mid-ventricular segments with preserved function of the apical segments, has been described.[9,10] We report a clinical case of a patient with an undiagnosed pheochromocytoma presenting with acute heart failure and an inverted-Takotsubo contractile pattern cardiomyopathy, and present a review of this reversible clinical syndrome.

Clinical Case

A 30-year-old man with no previous medical history presented to the emergency room with a 2-hour history of severe suprapubic and left lower quadrant abdominal pain. At emergency room triage, the patient was afebrile with a blood pressure of 128/72, heart rate of 83 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. Initial laboratory values revealed a significant leukocytosis with a white blood cell count of 29 600/μL, a neutrophilic predominance, and an elevated serum creatinine of 1.6 mg/dL. Blood cultures and urine cultures were collected. Chest radiography showed no evidence of acute cardiopulmonary disease. The patient was treated with ketorolac, hydromorphone, and ondansetron with moderate relief of his abdominal pain.

A computed tomography (CT) scan of his abdomen and pelvis was ordered. While ingesting oral contrast in preparation for the CT scan, the patient became acutely short of breath. On evaluation, the patient was tachycardic, tachypneic, and hypoxic. An arterial blood gas revealed a pH of 7.29, $PaCO_2$ 48 mm Hg, PaO_2 79 mm Hg, and an elevated arterial lactate of 4.6 mmol/L. Repeat chest radiography showed new bilateral basilar patchy opacities and small

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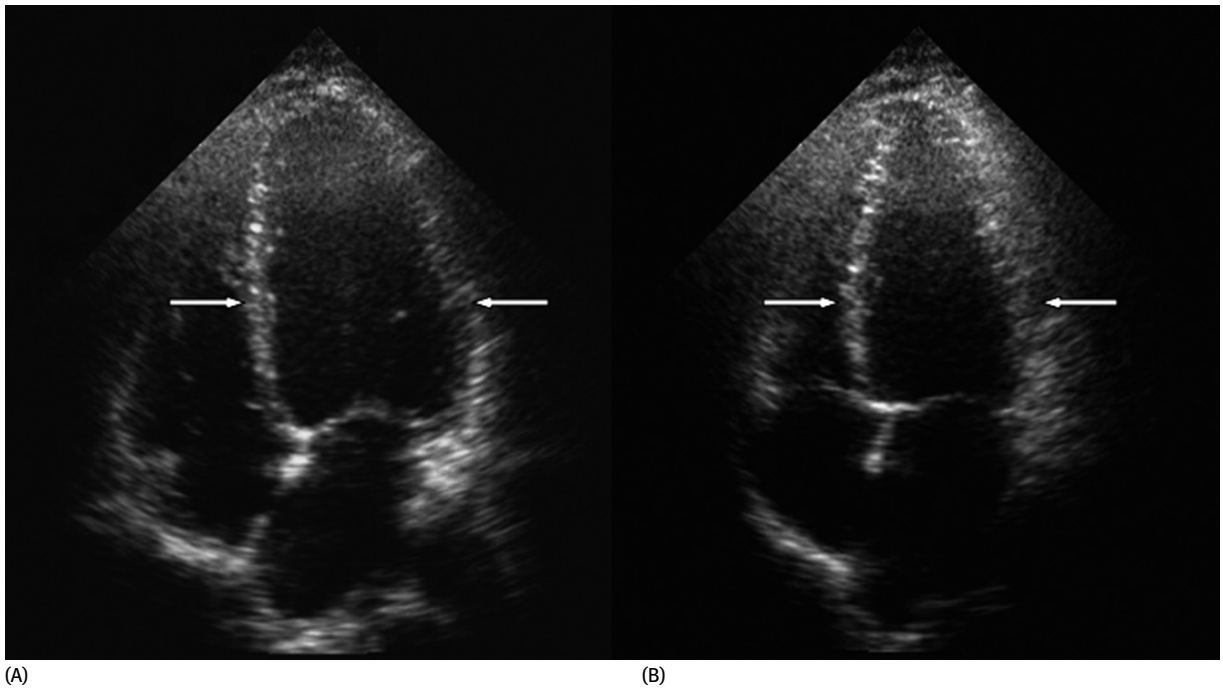
pleural effusions. ECG showed sinus tachycardia with 1 mm ST depressions in leads II, III, aVF, and V_3 through V_6. Initial cardiac enzymes were negative. The patient was started on noninvasive positive pressure ventilation, given intravenous furosemide, and transferred to the intensive care unit for closer monitoring. The initial impression was of acute respiratory failure possibly due to aspiration, pulmonary embolus, or acute heart failure.

Over the next 12 hours, the patient's clinical status improved dramatically, and he was weaned from noninvasive positive pressure ventilation to room air. Repeat laboratory results showed that his white blood cell count had fallen to within normal limits. However, he had elevated cardiac enzymes with a troponin I of 7.90 ng/mL (normal: < 0.40 ng/mL), creatinine kinase of 372 U/L (normal: 38–234 U/L). A transthoracic echocardiogram demonstrated severe hypokinesis of the basal segments of the anterior, inferior, and lateral walls with preserved function in the apical segments in an inverted-Takotsubo pattern (Figure 1). Overall estimated left ventricular ejection fraction was 35%. There was no significant valvular disease.

To evaluate hypoxia, the patient underwent a CT scan of the chest with intravenous contrast which was negative for pulmonary embolism. The CT extended down to the abdomen and pelvis, revealing a 3.8 $\times$ 3.3 cm left adrenal mass. To further delineate the mass, an magnetic resonance imaging (MRI) of the abdomen and pelvis was performed which confirmed a 3.4 $\times$ 3.7 $\times$ 3.4 cm left adrenal mass consistent with either pheochromocytoma or a degenerating lipid-poor adenoma (Figure 2).

A repeat transthoracic echocardiogram 48 hours after the initial study showed complete resolution of the previously-noted wall motion abnormalities with a normal ejection fraction of 55%. Given the patient's elevated cardiac markers and recent ventricular dysfunction, coronary evaluation with invasive coronary angiography was offered to the patient. However, due to the patient's age, lack of traditional coronary artery disease risk factors, and patient preference, coronary evaluation was undertaken with noninvasive CT angiography using a 64-slice CT scanner. The CT angiogram revealed anatomically normal coronary arteries with no atherosclerotic disease and a coronary calcium score of 0 using the Agatston method (Figure 3). Recent studies have demonstrated that the combination of a normal coronary CT angiogram and negative coronary calcium score has a negative predictive value near 100% for excluding obstructive coronary artery disease, when compared to conventional coronary angiography.[11–13]

Based on the patient's clinical history, acute heart failure syndrome, and transient wall motion abnormalities in the setting of normal coronary arteries, the presumptive diagnosis was one of an inverted-Takotsubo contractile pattern



(A) (B)

Figure 1. Apical 4-chamber view of transthoracic echocardiogram demonstrating hypokinesis of the basal segments (arrows) with preserved function in the apical segments. (A) diastole; (B) systole.

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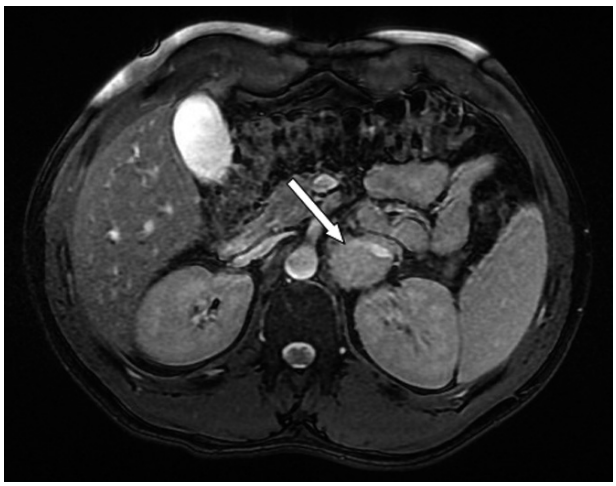


Figure 2. Unenhanced T2 axial MRI revealing a 3.4 cm × 3.7 cm × 3.4 cm left adrenal mass (arrow).

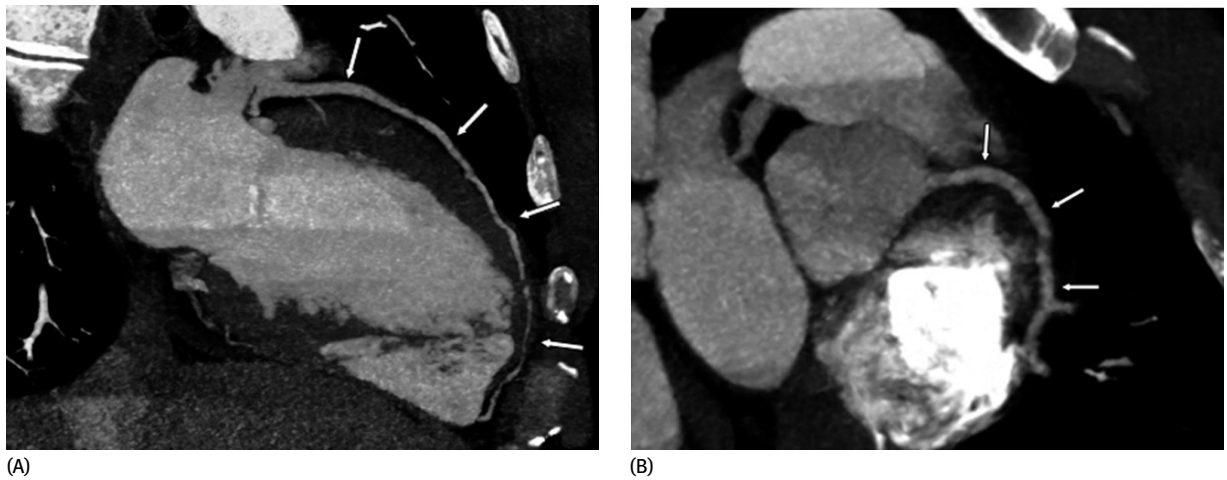
cardiomyopathy, possibly secondary to an occult pheochromocytoma. The recognition of the inverted-Takotsubo contractile pattern combined with the adrenal mass seen on abdominal imaging prompted further laboratory evaluation, which revealed markedly elevated serum and 24-hour urinary metanephrines and catecholamines (Table). One month later, the patient underwent an exploratory laparotomy and excision of the large left adrenal mass, with gross and microscopic pathology confirming pheochromocytoma (Figure 4).

Discussion

Pheochromocytomas have been known to cause a reversible cardiomyopathy dating back to 1969 when Wiswell et al studied a group of 13 patients with pheochromocytoma who had cardiac symptomology.[2] A total of 6 patients had initially presented with electrocardiogram changes including ST-elevations, ST-depressions, and T-wave inversions, causing concern of coronary insufficiency, which resolved following tumor removal. On autopsy, 5 patients were found to have focal areas of myocardial fibrosis with only minimal coronary artery atherosclerosis. Based on these findings, Wiswell et al concluded that patients with pheochromocytoma could have a reversible form of cardiomyopathy, without coronary artery obstruction, likely caused by elevated catecholamines.[2] However, it would not be until the late 1980s, with the more widespread use of cardiac imaging, that pheochromocytoma-induced cardiomyopathy, presenting with hyperkinesis of the basal segments and apical hypokinesis, was identified via

Table 1. Serum and Urinary Catecholamine Levels

	Patient's Values	Reference Range
Serum		
Normetanephrine (nmol/L)	12.60	0.00–0.89
Metanephrine (nmol/L)	1.66	0.00–0.49
Urine (24-h collection)		
Normetanephrine (μg/d)	3289	50–650
Metanephrine (μg/d)	878	30–350
Epinephrine (μg/d)	31	0–25
Norepinephrine (μg/d)	168	0–100
Dopamine (μg/d)	349	60–440



(A) (B)

Figure 3. Sample coronary computed tomography angiography with maximum intensity projections showing anatomically normal coronary arteries without atherosclerosis. (A) left anterior descending artery (arrows); (B) right coronary artery (arrows).

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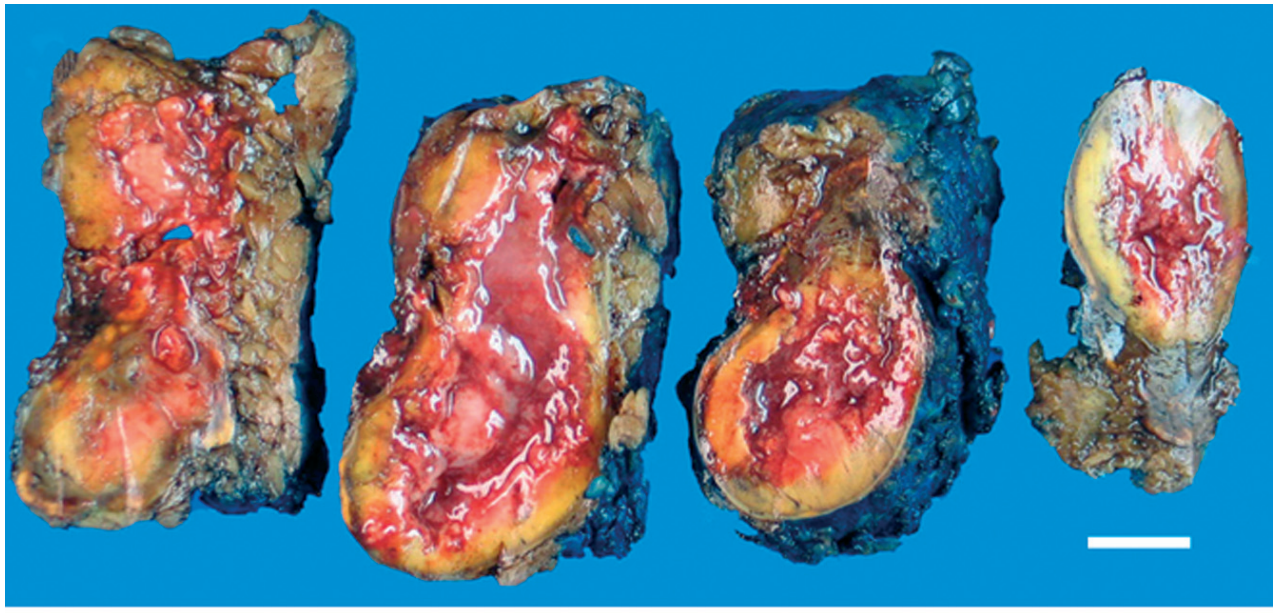
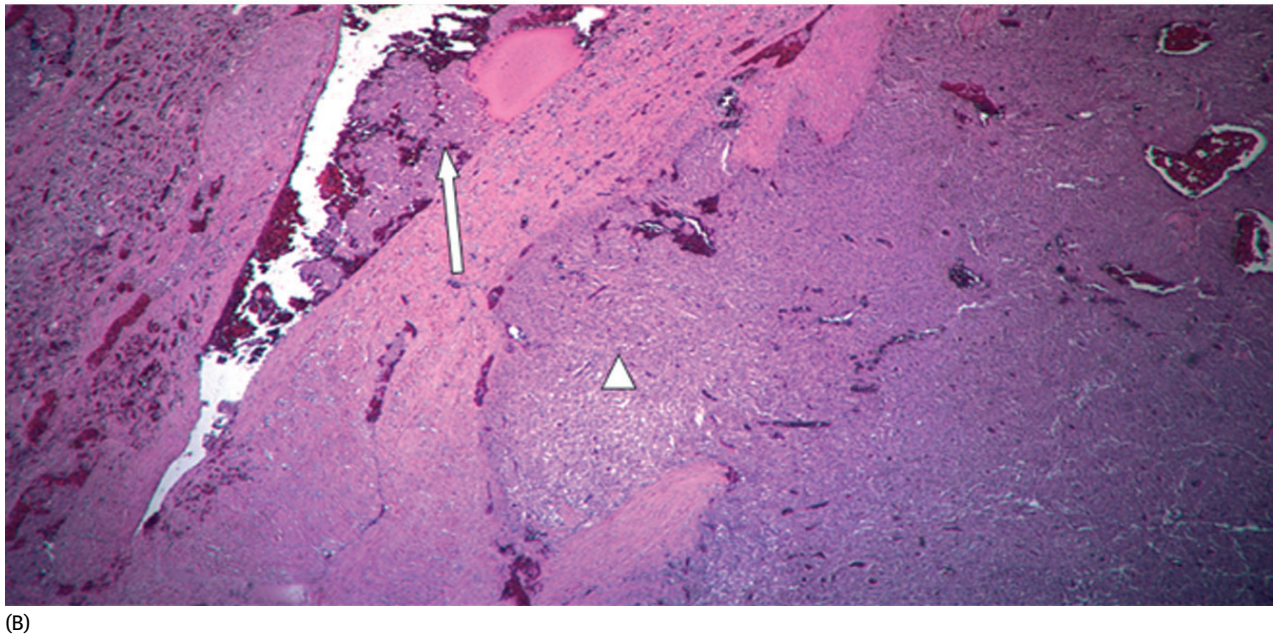


(A)



(B)

Figure 4. Gross and microscopic appearance of pheochromocytoma. (A) Soft, friable yellow-white tumor with areas of hemorrhage occupying the medulla of the left adrenal gland. Scale bar = 1 cm. (B) Microscopic appearance of pheochromocytoma with hematoxylin and eosin staining. Sheets of tumor cells (right side of picture) demonstrating both capsular (arrowhead) and vascular (arrow) invasion.

echocardiography and ventriculography.[14] The rapidly reversible left ventricular dysfunction seen with pheochromocytoma would later be characterized as Takotsubo cardiomyopathy when occurring in the setting of physiologic stress.

Takotsubo cardiomyopathy was first described in the Japanese literature in 1990 as a syndrome of reversible left ventricular dysfunction with apical ballooning.[8] Due to its hallmark bulging of the apex and compensatory hypercontraction of the basal segments, the shape of the heart was

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thought to be similar to that of a Japanese octopus trap, or "tako-tsubo," from which it subsequently derived its name. Although the prevalence of Takotsubo cardiomyopathy in the general population is unclear, it has been increasingly reported since its recognition as a clinical syndrome. In a review, Gianni et al found the prevalence of Takotsubo cardiomyopathy to be between 1.7% to 2.2% of patients who present with suspected acute coronary syndrome.[15] Takotsubo occurs most commonly in postmenopausal women between 60 to 70 years old and is often preceded by emotional or physical stress with associated elevation of plasma catecholamine levels.[16] The clinical syndrome of Takotsubo cardiomyopathy typically presents with signs and symptoms consistent with acute myocardial infarction, including chest pain and shortness of breath, ECG changes of ST-segment elevation or depression later evolving to diffuse T-wave inversions, and elevated cardiac enzymes.[16] Acute complications can also develop from the new onset left ventricular dysfunction including arrhythmias, pulmonary edema, and cardiogenic shock. Fortunately, outcomes are almost universally favorable, with a return of normal ventricular function in nearly all patients.[17]

Recently, a variant form of Takotsubo cardiomyopathy was recognized, in which patients present with hyperdynamic function of the apical segments, with hypokinesis of the basal and mid-ventricular segments.[9,10] Given its distinct basal involvement with apical and mid-ventricular sparing and its unique appearance on imaging, this type of transient left ventricular dysfunction was considered to be "atypical" or "inverted." Despite its only recent identification, inverted-Takotsubo may be more common than initially believed. In a prospective study of 3265 patients who presented with troponin-positive acute coronary syndrome, Kurowski et al found 35 cases of transient cardiomyopathy of which 21 (60%) had the classic apical wall motion abnormality while 14 (40%) had the inverted mid-ventricular pattern.[17]

There is currently no universal consensus for the diagnostic criteria of Takotsubo cardiomyopathy. Based on the proposed Mayo Clinic criteria, the diagnosis of Takotsubo requires meeting all 4 of the following: (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement with the regional wall motion abnormalities extending beyond a single epicardial vascular distribution, (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture, (3) new ECG abnormalities or elevation in cardiac troponin, and (4) the absence of pheochromocytoma and myocarditis.[18] This last requirement precludes the presence of pheochromocytoma; the reversible cardiomyopathy associated with pheochromocytoma, then, can only be described in terms of a typical or inverted-Takotsubo pattern. This point has been lost in some case reports that have claimed the diagnosis of Takotsubo cardiomyopathy secondary to a pheochromocytoma.[19,20]

In a review of the medical literature, the left ventricular dysfunction patterns associated with pheochromocytoma-induced cardiomyopathy have been heterogeneous.[4–7,19–26] Interestingly, over the past 2 years, there have been a disproportionate number of published case reports of pheochromocytomas presenting with the inverted-Takotsubo cardiomyopathy pattern, as in this patient.[19–25] A total of 7 different case reports recount the clinical course of patients who presented with signs and symptoms for an acute coronary syndrome only to later find normal coronary arteries. In these cases, transthoracic echocardiography revealed severe left ventricular dysfunction with akinesis of the basal and mid-ventricular segments, consistent with the inverted-Takotsubo pattern. With supportive care, which sometimes required intravenous pressors,[18–20] intra-aortic balloon pump,[21,22] or even extracorporeal membrane oxygenation,[23] patients had complete resolution of their condition. Further work-up would later discover an adrenal or extra-adrenal mass secreting excessive amounts of catecholamines leading to the diagnosis of pheochromocytoma.

It remains to be determined if the reversible cardiomyopathy of pheochromocytoma presenting in the inverted-Takotsubo pattern is a true epidemiologic phenomenon or merely publication bias given the only recent recognition of the inverted-Takotsubo cardiomyopathy. There are currently no published studies on the incidence and possible association of pheochromocytomas with either the typical or inverted-Takotsubo pattern. Whether the preference for pheochromocytoma-induced cardiomyopathy to present in the inverted-Takotsubo pattern has biologic plausibility has yet to be determined.

A physiologic explanation for the wall motion abnormalities seen in the typical and inverted patterns of Takotsubo cardiomyopathy has not been clearly established. Previous literature has suggested that differences in sympathetic innervation, β-receptor density, as well as regional differences in sensitivity to adrenergic stimulation may have a role. Disappointingly, animal studies on this topic have been equivocal and unable to provide a satisfactory answer.[27–30] Based on early studies performed on dogs, the sympathetic innervation of the left ventricle becomes increasingly sparse from the base to the apex.[27,28] One would suspect that this could potentially explain the typical left ventricular apical ballooning pattern with hyperkinetic basal walls. However, despite the regional differences in catecholamines, subsequent studies found a compensatory increased β-adrenergic receptor density in the cardiac apex.[29,30] Furthermore, in his examination of 26 anesthetized mongrel dogs, Mori et al showed that the apical myocardium was in fact more responsive to sympathetic stimulation.[30] Putting this together, these findings fail to provide a unifying explanation to elucidate the 2 clinical patterns of myocardial dysfunction seen in clinical practice.

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While pheochromocytomas have been known to cause a reversible cardiomyopathy for decades, the growing recognition of Takotsubo cardiomyopathy has revealed a likely connection among the 2 conditions. The similarities in the clinical presentations of pheochromocytoma and Takotsubo cardiomyopathy strongly support a shared pathophysiology implicating the role of catecholamines, via myocardial stunning or direct myocardial toxicity. Furthermore, with the routine and evolving use of cardiac imaging, the left ventricular dysfunction seen in pheochromocytoma-induced cardiomyopathy has been demonstrated to present in a similar fashion to that of Takotsubo, particularly in the inverted pattern. The increased frequency of published case reports of pheochromocytomas presenting with the inverted-Takotsubo cardiomyopathy pattern may reflect a newly recognized pathologic association, which warrants further investigation with larger scale epidemiologic studies.

References

1. 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(1):46–66. Review.
2. Wiswell JG, Crago RM. Reversible cardiomyopathy with pheochromocytoma. *Trans Am Clin Climatol Assoc*. 1969;80:185–195.
3. Wood R, Commerford PJ, Rose AG, et al. Reversible catecholamine-induced cardiomyopathy. *Am Heart J*. 1991;121(2 Pt 1) 610–613.
4. Schuiki ER, Jenni R, Amann FW, et al. A reversible form of apical left ventricular hypertrophy associated with pheochromocytoma. *J Am Soc Echocardiogr*. 1993;6(3 Pt 1):327–331.
5. Takizawa M, Kobayakawa N, Uozumi H, et al. 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(1): e15–e17.
6. Lassnig E, Weber T, Auer J, et al. Pheochromocytoma crisis presenting with shock and tako-tsubo-like cardiomyopathy. *Int J Cardiol*. 2009;134(3):E138–E140.
7. Von Bergen NH, Lyon JK, Edens, RE. Takotsubo-like cardiomopathy in a 17-year-old male with a pheochromocytoma. *Pediatr Cardiol*. 2009;30(2):184–187.
8. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. *Clinical Aspect of Mycardial Injury: From Ischemia to Heart Failure*. Tokyo, Japan: Kagakuhyouronsha; 1990;56–64.
9. Hurst RT, Askew JW, Reuss CS, et al. Transient midventricular ballooning syndrome: a new variant. *J Am Coll Cardiol*. 2006; 48(3):579–583.
10. Bonnemeier H, Schafer U, Schunkert H. Apical ballooning without apical ballooning. *Eur Heart J*. 2006;27(18):2246.
11. Ravipati G, Aronow WS, Lai H, et al. Comparison of sensitivity, specificity, positive predictive value, and negative predictive value of stress testing versus 64-multislice coronary computed tomography angiography in predicting obstructive coronary artery disease diagnosed by coronary angiography. *Am J Cardiol*. 2008; 101(6):774–775.
12. Leschka S, Scheffel H, Desbiolles L, et al. Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease. *Heart*. 2008;94(9):1154–1161.
13. Cademartiri F, Maffei E, Palumbo A, et al. Diagnostic accuracy of computed tomography coronary angiography in patients with a zero calcium score. *Eur Radiol*. 2010;20:81–87.
14. Shaw TRD, Bafferty P, Tait GW. Transient shock and myocardial impairment caused by pheochromocytoma crisis. *Br Heart J*. 1987;57(2):194–198.
15. Gianni M, Dentali F, Grandi AM, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systemic review. *Eur Heart J*. 2006;27(13):1523–1529.
16. Bybee KA, Kara T, Prasad A, et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med*. 2004;141(11): 858–865. Review.
17. Kurowski V, Kaiser A, von Hof K, et al. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest*. 2007;132(3):809–816.
18. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (tako-tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J*. 2008;155(3):408–417.
19. Di Valentino M, Balestra GM, Christ M, et al. Inverted takotsubo cardiomyopathy due to pheochromocytoma. *Eur Heart J*. 2008;29(6):830.
20. Jindal V, Baker ML, Aryangat A, et al. Pheochromocytoma: presenting with regular cyclic blood pressure and inverted takotsubo cardiomyopathy. *J Clin Hypertens*. 2009;11(2):81–86.
21. Sanchez-Recalde A, Costero O, Oliver JM, et al. Images in cardiovascular medicine. Pheochromocytoma-related cardiomyopathy: inverted Takotsubo contractile pattern. *Circulation*. 2006;113(17): e738–e739.
22. Kim HS, Chang WI, Kim YC, et al. Catecholamine cardiomyopathy associated with paraganglioma rescued by percutaneous cardiopulmonary support: inverted Takotsubo contractile pattern. *Circ J*. 2007;71(12):1993–1995.
23. Zegdi R, Parisot C, Sleilaty G, et al. Pheochromocytoma-induced inverted Takotsubo cardiomyopathy: a case of patient resuscitation with extracorporeal life support. *J Thorac Cardiovasc Surg*. 2008; 135(2):434–435.
24. Kimura S, Mitsuma W, Ito M, et al. Inverted Takotsubo contractile pattern caused by pheochromocytoma with tall upright T-waves, but not typical deep T-wave inversion. *Int J Cardiol*. 2009;139: e15–e17.
25. Cho DK, Kim JH, Chung N. Transient mid-ventricular ballooning cardiomyopathy associated with bladder pheochromocytoma. *Eur Heart J*. 2009;30(10):1202.
26. Ibanez B, Benezet-Mazuecos J, Navarro F, et al. Takotsubo syndrome: a Bayesian approach to interpreting its pathogenesis. *Mayo Clin Proc*. 2006;81(6):732–735.
27. Angelakos ET. Regional distribution of catecholamines in the dog heart. *Circ Res*. 1965;16:39–44.
28. Pierpont GL, DeMaster EG, Cohn JN. Regional differences in adrenergic function within the left ventricle. *Am J Physiol*. 1984;246(6 Pt 2):H824–H829.
29. Lathers CM, Levin RM, Spivey WH. Regional distribution of myocardial β-adrenoceptors in the cat. *Eur J Pharmacol*. 1986; 130(1–2):111–117.
30. Mori H, Ishikawa S, Kojima S, et al. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. *Cardiovasc Res*. 1993;27(2):192–198.

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