CASE CONFERENCES

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CASE 7—2015

Perioperative Considerations for a Cardiac Paraganglioma…Not Just Another Cardiac Mass

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ALTHOUGH INTRACARDIAC MASSES represent uncommon cardiac pathology, detailed knowledge of the implications of specific tumor types for anesthetic management is vital for the cardiac anesthesiologist. Cardiac masses may interfere with valve structure or function, invade across anatomic boundaries interfering with ventricular function or blood flow, or compromise coronary blood flow leading to ischemic-type myocardial dysfunction. Of particular interest are cardiac secretory tumors—these masses not only have local implications but also can result in severe systemic disease. Perhaps the most interesting of these masses is cardiac paraganglioma.

Paragangliomas are rare neuroendocrine tumors with the same morphology as pheochromocytomas, being made up of chromaffin cells. However, in contrast to pheochromocytomas, which arise from the adrenal medulla, paragangliomas arise from ganglia in the head and neck region or within thoracic or abdominal cavities.[1] When examined together with pheochromocytomas, paragangliomas have an incidence of about 10% that of pheochromocytomas.[2,3] Only a small percentage (3%) of all paragangliomas are thoracic in location,[4] and when contiguous with cardiac structures, they are referred to variably in the literature as "cardiac paraganglioma," "cardiac pheochromocytoma," "intrapericardial pheochromocytoma," or "mediastinal pheochromocytoma."[3,5–7] For clarity, the term "cardiac paraganglioma" is used here.

Cardiac paragangliomas may be functional or nonfunctional, depending on the degree to which they secrete catecholamines,[1] although symptom presentation is variable. Functional cardiac paragangliomas commonly arise from sympathetic ganglia associated with the aortic body or left atrium.[3] Although not always associated with the same degree of metabolic derangement as adrenal pheochromocytomas, cardiac paragangliomas lead to significant perioperative challenges.[3] The authors present a case of a catecholamine-secreting cardiac paraganglioma requiring resection with cardiopulmonary bypass (CPB) and discuss preoperative preparation of the patient, operative risk assessment, intraoperative transesophageal echocardiography (TEE) findings, and postoperative challenges in managing this complex pathology.

CASE REPORT

A 25-year-old woman presented to the hospital with a hypertensive crisis (highest blood pressure 202/122 mmHg) after a 2-year history of malignant hypertension, headaches, and palpitations. Investigation revealed markedly elevated serum normetanephrine and a 5 cm × 4 cm × 4 cm mass in the middle mediastinum, located caudal to the pulmonary artery bifurcation and aortic arch extending to the top of the left atrium (Fig 1). An endocrinologist was consulted for this presumed paraganglioma, and after 2 weeks of medical management, therapeutic levels of phenoxybenzamine (70 mg daily) and labetalol (50 mg daily) were achieved.

After uneventful induction of anesthesia with invasive monitoring, a complete TEE assessment according to the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists guidelines[8] revealed a large mass impinging on the left atrium and pulmonary arteries with preserved cardiac function (Figs 2–4). The mass was within the pericardium but did not arise from within the left atrium or pulmonary arteries. There was no significant obstruction to flow in pulmonary arteries or veins, and cardiac function was preserved.

Immediately after surgical incision, the patient became tachycardic and hypertensive (heart rate 130 beats/min, blood pressure 178/95 mmHg) despite continuous infusions of sodium nitroprusside and esmolol. The authors elected to use these drugs over phentolamine for ease of administration, rapid titratability, and ready availability from the pharmacy. When CPB was initiated without aortic cross-clamp, hypertension persisted. After tumor resection (Fig 5) and repair of the left atrium, norepinephrine and vasopressin infusions were required for maintenance of blood pressure and separation from CPB; transfusion of 450 mL of cell-salvaged blood, 1 unit of packed red blood cells, 1,200 mL of crystalloid, and 250 mL of 5% albumin was administered to restore intravascular volume. Hypotension persisted until postoperative day

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1053-0770/2602-0033$36.00/0
http://dx.doi.org/10.1053/j.jvca.2015.01.016
Key words: paraganglioma, catecholamine-secreting tumor

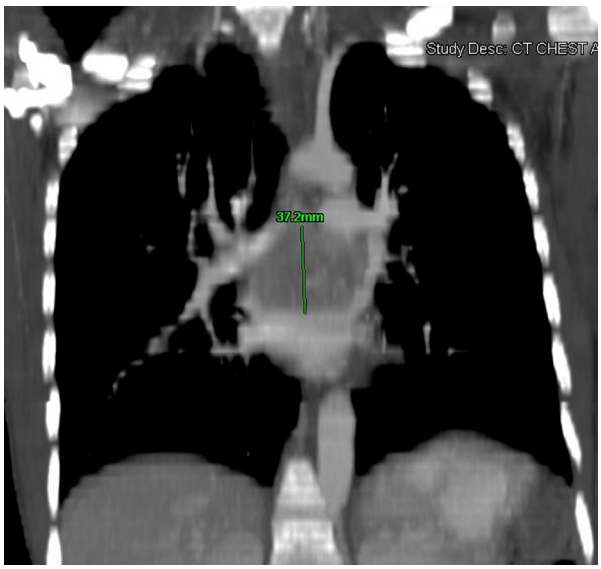

Fig 1. Computed tomography image depicting middle mediastinum tumor location. The maximum tumor diameter on this slice is indicated (37.2 mm).

6 in the intensive care unit, requiring support with fluid resuscitation and infusions of dobutamine, norepinephrine, and vasopressin. The patient initially was oliguric on arrival to the intensive care unit and on postoperative day 1, but responded with volume repletion. The patient required ongoing fluid resuscitation for 48 hours postoperatively and was oliguric during this period. She also required a dextrose infusion for 2 days postoperatively for hypoglycemia.

Transthoracic echocardiography performed on postoperative day 2 revealed new onset of severe tricuspid regurgitation (TR) and mildly depressed right ventricular (RV) function with a hyperdynamic left ventricle. Echogenic material was imaged at the tumor site adjacent to the left atrium consistent with postsurgical hemostatic material. Evaluated together with evidence of elevated left atrial pressures and slightly elevated pulmonary artery pressures, her transient TR was hypothesized to be a result of postoperative local inflammatory changes at the tumor site combined with transient post-CPB RV dysfunction. By postoperative day 7, her RV dysfunction and TR had resolved. The patient was discharged from the hospital on postoperative day 9 after resolution of TR.

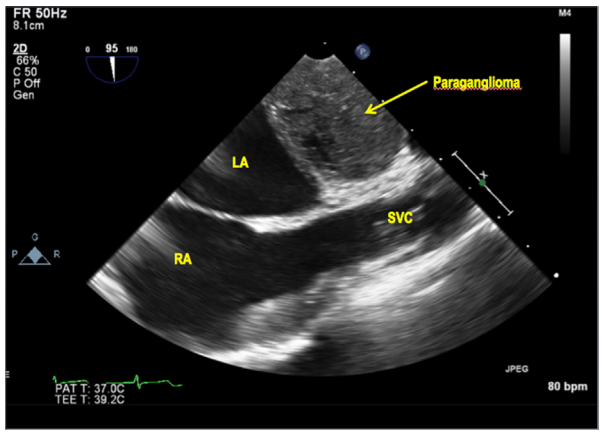

Fig 3. Midesophageal bicaval view showing compression of the left atrium (LA) by the paraganglioma and proximity to the superior vena cava (SVC). RA, right atrium.

DISCUSSION

How Should This Patient Be Prepared Preoperatively to Minimize Complications Related to Sympathetic Mediator Release?

Given the rarity of cardiac paragangliomas, expertise and knowledge surrounding anesthetic management for this tumor are limited. Preoperative preparation of the patient for resection of adrenal pheochromocytomas has been well described,[1] and the same guiding principles apply for a cardiac paraganglioma.[3] Management includes consideration for end-organ dysfunction resulting from hypertension (eg, myocardial dysfunction, cardiomyopathy, congestive heart failure, renal insufficiency, cerebrovascular events) and establishment of therapeutic alpha-blockade. Traditionally,

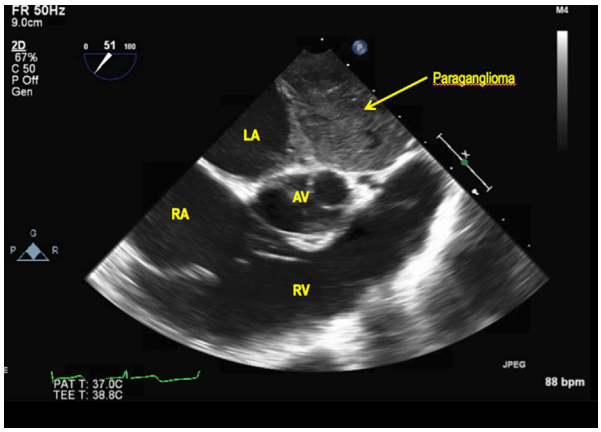

Fig 2. Midesophageal aortic valve (AV) short-axis view showing anatomic proximity of the paraganglioma to the left atrium (LA), AV, and RV outflow tract. RA, right atrium.

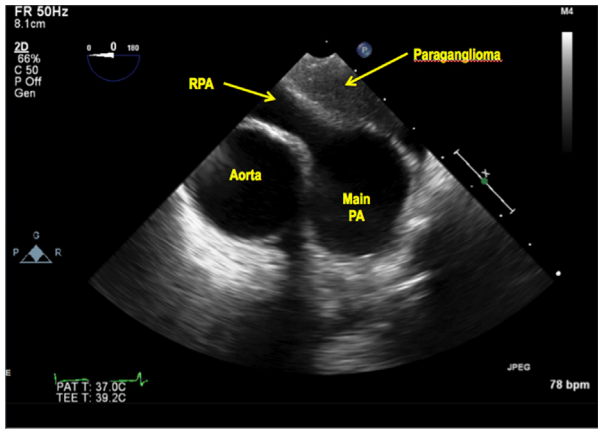

Fig 4. Midesophageal ascending aorta short-axis view showing compression of the right pulmonary artery (RPA) by the paraganglioma. PA, pulmonary artery.

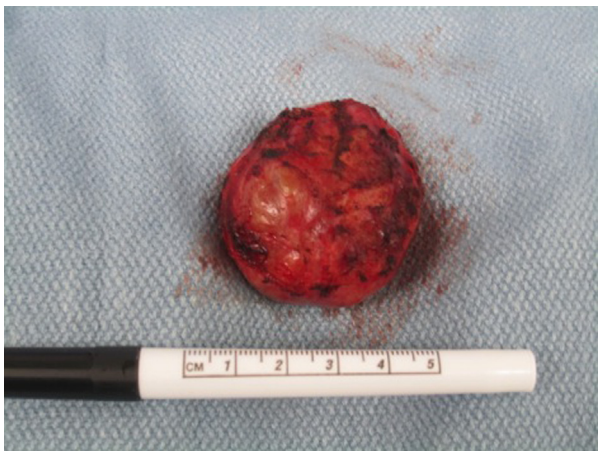

Fig 5. Tumor after resection. (Color version of figure is available online.)

adequacy of alpha-blockade has been assessed according to criteria established by Roizen et al,[1] as follows: (1) no blood pressure reading >160/90 mmHg in 24 hours before surgery, (2) the presence of orthostatic hypotension but with 80/45 mmHg as the lowest targeted blood pressure, (3) no ST-T wave changes on electrocardiogram for 1 week before surgery, and (4) no more than 1 premature ventricular contraction in 5 minutes. However, patients may be prepared for surgery safely in a less resource-intensive manner as an outpatient, provided that at least 10 to 14 days are allowed for alpha-blockade titration to allow for control of blood pressure, re-expansion of intravascular circulating volume, and control of symptoms.[4]

An additional concern with cardiac paraganglioma is the risk of patient exsanguination during resection. Because of their highly vascular nature, paragangliomas frequently invade surrounding structures, resulting in 7% to 18% intraoperative mortality from hemorrhage in the 3 largest case series reported.[5] Hemorrhage is poorly tolerated in the setting of a chronically hypertensive patient who arrives to the operating room intravascularly depleted, so preoperative and intraoperative volume expansion guided by central venous pressure, TEE assessment, or pulmonary capillary wedge pressure is advised. Multiple techniques have been used to facilitate complex resections, including total circulatory arrest and cardiac transplantation, although more easily accessible tumors may not require CPB.[1] In pelvic or head and neck paraganglioma, preoperative tumor embolization is often used to reduce hemorrhage risk at the time of surgery.[6–8] Tumor embolization for cardiac paragangliomas has been suggested[9–11] but is not widely used. A multidisciplinary planning session with the cardiac surgeon, anesthesiologist, perfusionist, and perioperative nursing teams before surgery facilitates adequate preparation of resources for intraoperative management.

What Is the Operative Risk Associated With This Procedure, and Can Standard Risk-Scoring Criteria and Calculations Apply?

In assessing operative risk for rare cardiac diseases or complex cardiac procedures, standard scoring systems often do not apply. The Society of Thoracic Surgeons online risk calculator (http://riskcalc.sts.org) can model operative morbidity and mortality accurately only for patients undergoing coronary artery bypass grafting or single-valve replacement surgery. The EuroSCORE (http://www.euroscore.org/calc.html) may underestimate operative risk significantly in patients for cardiac paraganglioma resection because this algorithm incorporates into the mortality score mainly patient factors and cardiac factors related to ischemic heart disease.

When a patient's primary risk factor is due to operative factors for a rare or complex procedure not related to ischemic heart or valvular disease, insufficient cumulative data to estimate risk of morbidity or mortality accurately are available. In examining adrenal pheochromocytomas and paragangliomas as a group, risk factors for intraoperative and postoperative events include large tumor size; prolonged duration of anesthesia; and increased levels of preoperative urinary epinephrine, norepinephrine, metanephrines, and vanillylmandelic acid.[2] For cardiac paragangliomas specifically, tumors located at the atrioventricular groove, invading the left ventricle or involving the coronary arteries, may have particularly high surgical mortality.[3] To minimize operative risk for this patient, therapeutic alpha-blockade was established preoperatively, indicated by the onset of orthostatic hypotension and resolution of palpitations and headaches. Adequate availability of blood products and vascular access were ensured, and intensive hemodynamic management was maintained intraoperatively and postoperatively. Cell salvage was used in the present case; however, when cell salvage is used during resection of a catecholamine-secreting tumor, generous irrigation of the surgical field with normal saline should be performed to ensure washing out catecholamines. If autotransfusion of cell-salvaged blood is conducted, close hemodynamic monitoring is particularly important because catecholamines may remain in the cell-salvaged blood.

What Findings Should Be Assessed on Intraoperative TEE?

Although preoperative imaging with computed tomography or magnetic resonance imaging elucidates tumor location and potential invasion into cardiac structures, TEE is the ideal modality to assess for associated hemodynamic effects. Cardiac paragangliomas typically are located in the left atrium or aortic root, but lesions may involve any cardiac chamber or great vessel.[10] A careful evaluation of all involved cardiac structures is essential because complete resection and reconstruction of these sites are necessary. Preoperative TEE should proceed according to the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists guidelines,[8] paying particular attention to areas of tumor involvement and resulting abnormal valve structure and function, inflow and outflow of cardiac chambers, and ventricular function. Specific findings of interest are related to tumor location. For example, distortion of the mitral valve apparatus and regurgitation may result from a tumor located in the atrioventricular groove.[1] Regional wall motion abnormalities may indicate tumor invasion into coronary arteries. Depending on the structure in question, direct impingement on the atria or great vessels may cause flow disturbance and an increase in upstream pressures, resulting in pulmonary hypertension, superior vena cava

syndrome, pulmonary venous inflow obstruction, or tamponade physiology. The presence of flow acceleration on color-flow Doppler should alert the echocardiographer to the potential for obstructive pathology, and further examination with spectral Doppler should be performed if appropriate.

TEE also is useful for reassessing volume status because these patients may arrive in the operating room with severe intravascular volume depletion, despite alpha-blockade therapy. Patients also may have a baseline cardiomyopathy related to prolonged adrenergic stimulation of the heart. These findings are useful in anticipating difficult separation from CPB.

After tumor resection, repeat examination of the cardiac structures in question should occur, with particular attention paid to possible abnormal communications between cardiac chambers (eg, atrial septal defects, ventricular septal defects, shunts). The adequacy of surgical resection and residual tumor should be evaluated because compete resection is the only effective treatment for these tumors, and recurrence has a poor prognosis.[10]

What Postoperative Challenges Can Be Expected After Tumor Resection?

After functional paraganglioma resection, the 3 major postoperative challenges are (1) blood pressure support for hypotension resulting from residual alpha-blockade, (2) repletion of intravascular volume, and (3) treatment of hypoglycemia. Although the differential diagnosis for hypotension in a patient after cardiac surgery remains broad, a major contributor after paraganglioma resection is residual alpha-blockade. Phenoxybenzamine nonselectively and noncompetitively blocks alpha-adrenergic receptors, rendering patients resistant to the effects of catecholamines until the drug is cleared.[1] In the case of phenoxybenzamine, this state may be prolonged owing to a drug half-life >24 hours.[1] Treatment with high doses of direct-acting vasoconstrictors, such as norepinephrine, may be required to overcome these effects. The addition of vasopressin may be useful (0.01-0.04 units/min) because vasoconstriction by this drug is mediated by V1 receptors on vascular smooth muscle cells,[12,13] not affected by alpha-blockade. Selective $alpha_1$-adrenergic antagonists such as doxazosin, prazosin, or terazosin may be preferred to phenoxybenzamine because these agents are competitive agonists, with half-lives as short as 2 to 3 hours in the case of prazosin.[1] Although potentially shortening the postoperative duration of hypotension, selective alpha-blockade may be less effective at blunting episodes of intraoperative hypertension,[14] and debate concerning the optimal agent continues. In the post–cardiac surgery setting, hypotension may be multifactorial in nature, and the solitary treatment of residual alpha-blockade is too simplistic an approach in this setting.

The postoperative course of the present patient also was complicated by intermittent oliguria, likely as a result of decreased perfusion pressure in the setting of a chronically hypertensive patient and hypovolemia. Fluid repletion in the setting of RV dysfunction can be challenging, and this patient initially was treated with a dobutamine infusion to avoid fluid overloading the right ventricle, while aiding filling of the underfilled left ventricle (by transthoracic echocardiography assessment). Over the course of several days, with cautious volume loading, the patient's urine output improved, and transient prerenal renal dysfunction resolved.

Lastly, after functional paraganglioma resection, patients are at risk for hypoglycemia for several days postoperatively and may require intravenous dextrose treatment. Elevated catecholamine levels preoperatively inhibit insulin release, and, consequently, hyperglycemia before surgery is common, although it rarely requires treatment with insulin.[1] After tumor removal, the sudden decrease in catecholamines causes rebound hyperinsulinemia and hypoglycemia. Prolonged emergence from anesthesia or altered mental status may result. The present patient required an intravenous dextrose infusion for 2 days postoperatively to maintain blood glucose >70 mg/dL. Blood glucose levels should be monitored closely after tumor removal in anticipation of this complication.

CONCLUSIONS

The authors reported the successful resection and perioperative management of a cardiac paraganglioma in a 25-year-old woman. Although cardiac paragangliomas are rare, knowledge regarding unique aspects of secretory tumor pathology is key to optimization of the patient during the perioperative course. Risk factors for intraoperative and postoperative events that have been identified for pheochromocytomas in general include large tumor size; prolonged duration of anesthesia; and increased levels of preoperative urinary epinephrine, norepinephrine, metanephrines, and vanillylmandelic acid.[2] For cardiac paragangliomas, tumors located at the atrioventricular groove invading the left ventricle or involving the coronary arteries may have particularly high surgical mortality.[1] Although the exact perioperative risk is difficult to quantify, risk can be minimized by preoperative optimization of the patient with alpha-blockade, accurate delineation of local tumor hemodynamic effects by TEE, anticipation of massive intraoperative blood loss, and treatment of postoperative hypotension and hypoglycemia in an intensive care unit setting.

COMMENTARY 1*

Cardiac paragangliomas are rare neuroendocrine tumors arising from the chromaffin cells of the sympathetic ganglia and are related cytologically to pheochromocytomas. Of all primary cardiac tumors, $<1\%$ are paragangliomas, with an incidence of 1.5 to 9 per 1 million.[10,16] These paragangliomas can cause significant morbidity and mortality related to compression or invasion of cardiac structures such as coronary arteries and cardiac chambers or through systemic effects of the catecholamines they secrete. These cases represent significant challenges to the anesthesiologist in the perioperative period and require multidisciplinary input for optimal care. A review of reported cases by Khan et al[17] found that cardiac paragangliomas were more common among female patients (55%) and more likely to be located in the left atrium (38%). Most were likely to be pericardial, locally invasive, and secreting vasoactive substances. Although most paragangliomas are sporadic, one-third have germline mutations of susceptibility genes such as those in the succinate dehydrogenase subunit complex.[18] The usual presentation of adrenal and extra-adrenal secretory tumors

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is refractory hypertension along with headaches and palpitations; biochemical analysis of degradation products of catecholamines secreted by these tumors is the cornerstone of diagnosis.[19] The advent of the metaiodobenzylguanidine scan significantly improved the ability to diagnose metastatic disease, which is critical because metastatic disease and intracardiac location are correlated strongly with negative outcomes.

Surgical treatment is the definitive treatment for cardiac paragangliomas, and mortality rates have been on a downward trend. After complete surgical excision, 10-year survival is estimated to be >80%, although the nearly 50% recurrence rate requires ongoing postoperative surveillance.[20] Gerlach et al described an interesting case of a woman with mediastinal paraganglioma who presented with classic symptoms, and a large tumor was diagnosed in the mediastinum adjacent to the left atrium. Based on the findings of Kinney et al,[2] the patient presented acceptable risk for attempted resection (size <6 cm), although circulating levels of catecholamines and duration of anesthesia were not reported. The authors correctly pointed out the inadequacy of the Society of Thoracic Surgeons scoring system and the EuroSCORE system to assess risk for their patient.

Patients with cardiac paragangliomas represent a fragile subpopulation in whom preoperative preparation is essential, as outlined by Gerlach et al. Bruynzeel et al[21] identified large tumor size, mean arterial pressure >100 mmHg, elevated norepinephrine levels, and more profound postural hypotension after treatment as risk factors for hemodynamic instability during surgical resection. Alpha-blockade using phenoxybenzamine has been the cornerstone of therapy, with therapeutic endpoints as described by Roizen and referenced by the authors. However, the duration of therapy (7-14 days) and its conduct on an inpatient basis has been debated.[22] Other authors successfully reported use of doxazosin and prazosin for reasons of a shorter duration of action and cost-effectiveness.[15,23] The addition of beta-blocker therapy in patients with preserved cardiac function helps control tachycardia and myocardial oxygen demand. Calcium channel blockers such as nifedipine, nicardipine, and verapamil have been used increasingly in recent years as well.[24] Another elegant agent in the arsenal against these tumors is metyrosine, a tyrosine analog that inhibits catecholamine synthesis. It has been used to reduce catecholamine stores, resulting in smoother hemodynamics, especially in patients with high catecholamine levels or patients with phenoxybenzamine intolerance.[25] Successful use of urapidil, magnesium, and octreotide also has been reported.[26] No clear consensus exists on the superiority of one agent over another in the literature, and practice is guided by institutional and clinician preference. The presence of a vigilant and skilled anesthesia team along with expeditious surgical resection likely is more contributory to a positive outcome than the drug combination used.

COMMENTARY 2[†]

Cardiac paragangliomas are rare masses that can cause physiologic disturbances because of catecholamine secretion or compression of surrounding structures. Hemodynamic effects can be attributed to numerous factors, including direct compression of cardiac structures, catecholamine-induced cardiomyopathy, and hypertension secondary to catecholamine release followed by hypotension after tumor removal. A multidisciplinary approach to perioperative care is highly recommended because the patient undergoes hemodynamic, metabolic, and cardiac structural changes during the perioperative period. Gerlach et al described the case of a young woman with an intrapericardial paraganglioma causing malignant hypertension from catecholamine secretion and provided a review of the perioperative care of these patients.

The present case raises 2 important issues pertinent to hemodynamic management and intraoperative imaging. First, volume expansion is an important component to the perioperative care of these patients. Volume expansion is initiated preoperatively and continued throughout the intraoperative and postoperative periods. Because of the excessive catecholamine secretion, the systemic vascular resistance is increased, and the patient has intravascular depletion despite the presence of systemic hypertension. After tumor removal, catecholamine production ceases, systemic vascular resistance decreases, and the patient's intravascular volume status is revealed by the hypotension that ensues. Many tools are available to guide fluid management. Variation in stroke volume and pulse pressure may be used to guide fluid management and have been shown to be accurate in open-chest conditions.[27] However, these measures are influenced by respiratory mechanics[28,29] and may be inaccurate in the presence of diastolic dysfunction.[30] Additionally, TEE can be used to assess fluid responsiveness. Global end-diastolic volume and respiratory variation in the left ventricular outflow tract velocity time integral have been shown to predict fluid responsiveness reliably in cardiac surgery.[31] However, care must be taken in the assessment of these parameters because compression caused by the cardiac paraganglioma or concurrent right heart dysfunction can result in inaccurate interpretations of these monitoring tools but would be recognized on TEE.[32]

Second, this case emphasizes the important use of perioperative echocardiography in a patient undergoing cardiac surgery. Preoperative echocardiography assessment should include a comprehensive evaluation of compressive features of the tumor and effect on surrounding structures. Various cardiomyopathies can develop from paragangliomas and should be characterized to optimize the perioperative plan. Postoperative echocardiography should be used early in the setting of acute hypotension of uncertain etiology.[33] The present patient had persistent hypotension despite aggressive intravascular volume replacement and vasopressor therapy after surgery. As a result, transthoracic echocardiography was performed that revealed new-onset TR, RV hypokinesis, and hemostatic material near the left atrium. Inotropic support was initiated, with ultimate resolution of RV dysfunction and TR. The authors were able to recognize an additional reason for hypotension and decreased cardiac output in the setting of residual phenoxybenzamine and decreased intravascular volume, both known causes of hypotension after paraganglioma resection. Without the use of echocardiography, RV dysfunction may not have been a presumed cause of hypotension in this young patient who showed normal cardiac function on intraoperative TEE. Additionally, postoperative changes such as pericardial effusion or compression of cardiac

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structures from hemostatic materials are recognized easily with TEE and are reversible causes of hypotension.

Although rare, cardiac paragangliomas present unique challenges because of catecholamine secretion and their compressive nature. A multidisciplinary approach with a detailed perioperative plan that includes expeditious surgery, echocardiographic imaging, and use of readily available hemodynamic medications, as the authors described, is essential in ensuring optimal outcomes.

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