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*Published in:*
Journal of cardiothoracic and vascular anesthesia

*DOI:*
10.1053/j.jvca.2021.03.034



*Publication date:*
2021

Journal of Cardiothoracic and Vascular Anesthesia 35 (2021) 3423–3433

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Case Conference

# Pheochromocytoma Resection in a Patient With Chronic Thromboembolic Pulmonary Hypertension and Thrombocytopenia

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*Key Words:* Pheochromocytoma; chronic thromboembolic pulmonary hypertension; right ventricular dysfunction

PHEOCHROMOCYTOMAS are rare catecholamine-secreting neuroendocrine tumors that can produce life-threatening cardiovascular instability.[1,2] Preoperative management with alpha-blockade and intravascular volume expansion are crucial to intraoperative hemodynamic management, given the risk of catecholamine surges with induction of anesthesia, intubation, surgical incision, insufflation, and tumor manipulation. Intraoperative pheochromocytoma resection management focuses on the goals of maintaining hemodynamic stability in the face of catecholamine surge. After resection, patients are at risk of systemic hypotension related to catecholamine withdrawal, especially in highly active pheochromocytomas.[3]

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication in patients with thromboembolic disorders. Incomplete resolution of acute pulmonary emboli organize into fibrotic material, obstructing large pulmonary arteries and distal small vessels, leading to significant pulmonary hypertension (pHTN) and often right ventricular (RV) failure.[4,5] Perioperative management of pHTN consists of minimizing pulmonary vascular resistance (PVR) by avoiding anxiety, pain, hypoxia, hypercarbia, acidosis, and hypothermia.[6] The most significant perioperative complication of severe pHTN is development or exacerbation of RV failure.[6] In patients with severe pHTN, systolic right coronary artery blood flow is impeded in direct proportion to RV pressure and RV hypertrophy.[7] Subsequently, perioperative management of RV failure hinges on RV pressure reduction through limited fluid administration, reduction in PVR, support of RV contractility, and maintenance of right coronary blood flow through adequate systemic vascular resistance (SVR).[3,7]

Perioperative management goals in a patient with both pheochromocytoma and CTEPH are often at odds. For instance, traditional perioperative management of a pheochromocytoma resection requires alpha-blockade and volume expansion, a potentially dangerous management strategy in the setting of CTEPH-induced RV dysfunction. Treating pheochromocytoma-induced intraoperative tachycardia with beta-blockade in a patient with CTEPH and RV dysfunction may reduce cardiac output and SVR, dangerously lowering RV perfusion. The authors present a complex case of a patient with

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https://doi.org/10.1053/j.jvca.2021.03.034
1053-0770/

CTEPH and idiopathic thrombocytopenia undergoing adrenalectomy for pheochromocytoma.

## Case Report

A 38-year-old, 82- kg, 171-cm (body mass index 28) man with neurofibromatosis type 1 (NF1) presented to the anesthesia preoperative medicine clinic for evaluation for right adrenalectomy due to pheochromocytoma. Before clinic presentation, the patient was admitted to an outside hospital one month earlier with a small bowel obstruction related to an enlarging adrenal mass first identified incidentally six years prior by a computed tomography scan. During this admission, biochemical studies, including plasma free metanephrines of 809 pg/mL (normal ≤57 pg/mL) and plasma free normetanephrines of 2,379 pg/mL (normal ≤148 pg/mL), were obtained. Magnetic resonance imaging revealed a right adrenal mass measuring 5.2 × 5.0 × 5.0 cm. Pheochromocytoma was diagnosed. After medical treatment and nonsurgical resolution of the partial bowel obstruction, the patient was discharged and referred to the authors' institution's endocrine surgeon for evaluation for adrenalectomy.

In the preoperative medicine clinic, the patient exhibited a blood pressure (BP) of 124/63 mmHg, a heart rate of 101 beats/min, normal sinus rhythm, and a peripheral oxygen saturation ($SpO_2$) of 92% on room air. He was noted to have mild non-pitting edema to the ankles bilaterally, two-pillow orthopnea, and dyspnea on exertion precluding him from achieving >4 metabolic equivalents. The patient had a medical history of antiphospholipid antibody syndrome (APLS) with recurrent deep vein thrombosis on warfarin, with an inferior vena cava filter previously placed and an international normalized ratio (INR) goal of 3-to-4. In addition, the patient developed CTEPH, which was treated with thromboendarterectomy. Subsequent management included serial pulmonary artery balloon angioplasties, the last of which was performed four months before his clinic visit. He required 2-to-3 L/min of oxygen per nasal cannula at night to maintain normal saturations and was on a stable regimen of riociguat, 2 mg three times daily and ambrisentan, 10 mg daily. The patient had associated right heart failure managed with eplerenone, 37.5 mg daily, metolazone, 2.5 mg daily, and bumetanide, 2 mg twice daily. He also had a medical history of idiopathic thrombocytopenia purpura (ITP), well-controlled reflux, and asthma with an albuterol inhaler. Transthoracic echocardiography (TTE) and right heart catheterization had been obtained one month before his clinic visit. TTE was notable for right atrium and RV dilation and systolic flattening of the ventricular septum, with normal left ventricular function.

Given the risks of alpha-blockade and intravascular volume expansion required for preoperative preparation of patients with pheochromocytoma, he was admitted to the cardiothoracic surgical intensive care unit (ICU) approximately one week before his scheduled procedure for pulmonary artery catheter (PAC)-directed titration of alpha-blockade and volume management. On the day of admission, the patient underwent right heart catheterization with PAC insertion. Right heart catheterization showed RV pressure of 66/6 mmHg, pulmonary artery pressure of 62/21 mmHg, with mean pulmonary artery pressure (mPAP) of 44 mmHg and a pulmonary capillary wedge pressure of 21 mmHg. Following the procedure, the patient was started on therapeutic heparin infusion at 14 U/kg/hr. The initial platelet count on admission was 154,000 platelets/μL. The alpha-blockade was initiated on hospital day one with doxazosin and orthostatic BPs, and HRs were obtained twice daily. The alpha-blockade slowly was increased with the goal of inducing orthostasis while maintaining a mean arterial pressure (MAP) >70 mmHg to maintain RV perfusion. The patient's platelet count was monitored closely during admission due to his history of ITP and APLS. On hospital day four, the platelet count declined to 30,000 platelets/μL. The patient was evaluated for heparin-induced thrombocytopenia type II. The heparin infusion was discontinued, an argatroban infusion was started, and both platelet factor 4 and serotonin release assays were drawn.

On hospital day seven, diuresis was resumed due to worsening hypoxia and dyspnea requiring continuous 3 L/min oxygen per nasal cannula presumed due to poorly tolerated volume expansion. In spite of diuresis, the patient's weight increased by 6.5 kg from admission until the time of surgery. On hospital day seven, the platelet count was noted to be 23,000 platelets/μL. The platelet factor 4 assay returned and was determined to be normal (0.368 optical density), and the serotonin release assay ultimately was negative. Hematology service was consulted. They considered a diagnosis of immune-mediated thrombocytopenia, given the patient's history of APLS, and recommended intravenous immune globulin (IVIG) and platelet transfusion therapy before surgery. From a nadir of 23,000 platelets/μL, the platelet count increased to 50,000 platelets/μL after IVIG therapy and transfusion of 1 unit of apheresed platelets.

On hospital day eight, the patient underwent laparoscopic right adrenalectomy for pheochromocytoma resection. The argatroban infusion was discontinued ten hours before surgery. On the morning of surgery, the platelet count was 44,000 platelets/μL without additional transfusions. Given the extensive preparation with alpha-antagonists and volume expansion using invasive monitoring, as well as the patient's response to platelet transfusion, a collaborative decision to proceed with the surgery was made by the anesthesiologist and surgeon.

The patient was premedicated with midazolam in the preoperative area, and standard American Society of Anesthesiologists monitors plus radial arterial line and PAC were utilized for continuous cardiac output (CCO) and mPAP monitoring before induction. Large-bore peripheral intravenous (IVs) access was obtained due to high risk of intraoperative blood loss.

The patient was pre-oxygenated with an $F_IO_2$ of 1.0. A mixed inhalation and IV induction was performed using sevoflurane, propofol, and fentanyl. Mask ventilation was difficult and required two providers, resulting in a desaturation to an $SpO_2$ of 70%. After successful intubation, the patient's $SpO_2$ improved to 88%, but bilateral wheezing was auscultated and treated with albuterol, with resolution of hypoxia. Two mg of

IV bumetanide were administered shortly after induction due to appreciable hypoxia in the setting of known pulmonary edema. Initial arterial blood gas (ABG) showed the partial pressure of arterial carbon dioxide ($PaCO_2$) of 51 mmHg with a minute ventilation of 11.2 L/min. The partial pressure of arterial oxygen ($PaO_2$) was 156 mmHg on an $F_IO_2$ of 1.0 and positive end-expiratory pressure (PEEP) of 10 cm $H_20$. The patient was maintained on these ventilator settings throughout the case. Subsequent ABGs would show similar values for the duration of the case.

Paralysis and general anesthesia were, respectively, maintained with rocuronium and sevoflurane. A transesophageal echocardiography (TEE) probe was inserted after induction, revealing normal biventricular function without regional wall motion abnormalities throughout the entirety of the case. A small thrombus was visualized on the tip of the PAC (Fig). Significant systemic and pHTN occurred during incision and insufflation, which were treated with IV boluses of propofol, fentanyl, and an increase inhaled volatile anesthetic administration. Small doses of IV vasopressin were used to maintain MAP >70 mmHg. The cardiac index ranged between 2.2 to 3.5 L/min/$m^2$ for the duration of the case, with the cardiac index correlating with the rise and fall of MAP and mPAP. Vital signs oscillated in a sinusoidal pattern during tumor dissection, with apex MAPs and mPAPs reaching 99 mmHg and 66 mmHg, respectively. Please refer to Table 1 for the temporal relationship among vital signs, medications administered, and intraoperative events.

Surgical dissection was complicated by adrenal capsular hemorrhage resulting in MAPs and mPAPs in the low 60s and 30s, respectively, despite intermittent administration of vasopressin and reduction of end-tidal sevoflurane to 1.3%. Two units of apheresed platelets, two units of fresh frozen plasma, and multiple crystalloid boluses were administered in conjunction with intermittent vasopressin boluses. Surgical hemostasis was achieved. Thromboelastogram showed no abnormalities. Post-hemorrhage hemoglobin was 9.7 g/dL after 600 mL of estimated blood loss. No packed red blood cells were transfused at this time. MAPs greater than 70 mmHg were maintained with intermittent blousing of vasopressin and 1.0 g of calcium chloride. There were no further surgical complications.

ABG during surgical closure obtained with an $F_IO_2$ of 1.0, minute ventilation of 11.2 L/min, and a PEEP of 10 $cmH_2O$ revealed a pH of 7.32, a partial pressure of arterial carbon dioxide of 43 mmHg, $PaO_2$ of 132 mmHg, and a lactate of 0.9 mmol/L. Due to a $PaO_2/F_IO_2$ ratio of 132, the patient was taken to the ICU, intubated, and sedated without the need for vasoactive medications.

On hospital day nine (postoperative day one), the patient tolerated a spontaneous breathing trial on minimal $F_IO_2$ and was extubated to Venturi mask with adequate oxygenation. TTE showed a flattened septum with RV pressure overload, a moderately dilated RV, a moderately reduced RV function, and an estimated RV systolic BP of at least 50 mmHg, consistent with moderate pHTN. Diuresis was restarted with the patient's home regimen. He was restarted on heparin infusion on postoperative day one without signs of postoperative bleeding and was bridged back to his home warfarin with an INR goal of 3-to-4. Thrombocytopenia did not recur. Platelet count continued to increase throughout his hospital stay and recovered to 295 platelets/μL at discharge.

On hospital day ten (postoperative day two), the patient developed splinting with atelectasis requiring bilevel positive

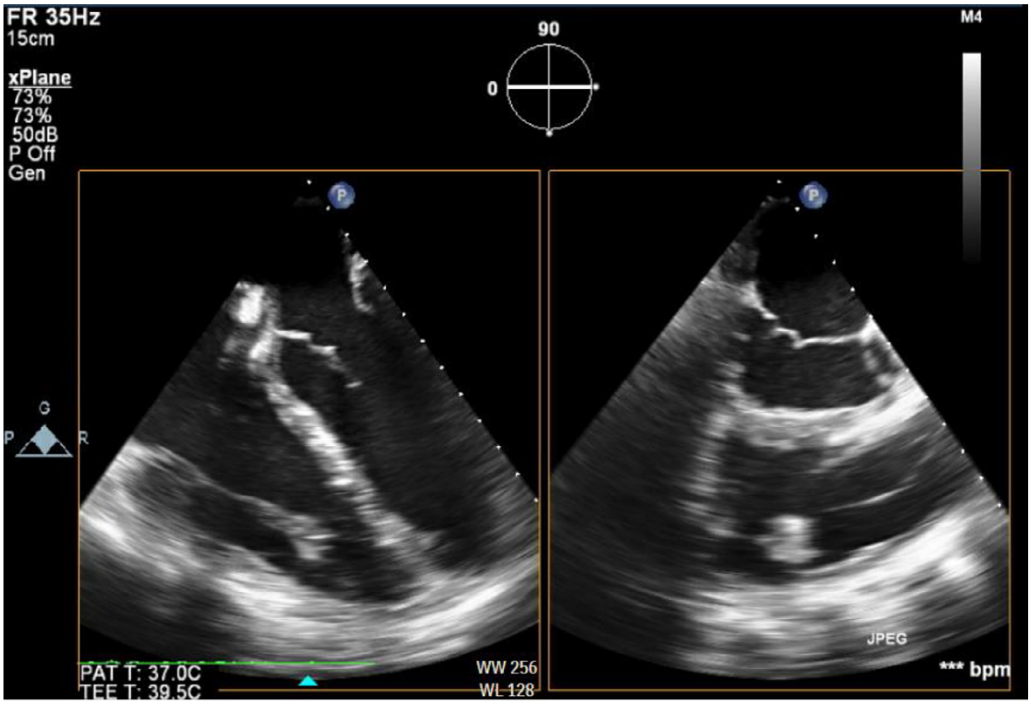


Fig. Transesophageal echocardiographic image showing small thrombus present on the tip of the pulmonary artery catheter.

Table 1
Important Perioperative Events

| Time | Perioperative Event | MAP, mmHg | mPAP, mmHg | HR, sinus | Treatment |
|---|---|---|---|---|---|
| 1436 | Preinduction | 78 | 56 | 102 | - |
| 1445 | Postinduction | 60 | 45 | 85 | 1 unit of vasopressin administered. |
| 1537 | Incision | 105 | 66 | 100 | 20 mg of propofol administered. |
| 1545 | Insufflation | 93 | 55 | 98 | - |
| 1615 | Tumor dissection apex | 99 | 66 | 110 | 50 μg of fentanyl administered. Increased $ET_{Sevo}$ 1.8%. |
| 1647 | Tumor dissection nadir | 71 | 61 | 103 | 0.5 units of vasopressin administered. |
| 1712 | Onset capsular hemorrhage | 61 | 49 | 113 | 1.5 units of vasopressin administered. Decreased $ET_{Sevo}$ to 1.3%. |
| 1713-1736 | Continued capsular hemorrhage | 63 | 52 | 115 | 2 units of FFP, 2 units of plts, and 900cc of lactated ringers administered |
| 1737 | Tumor manipulation | 125 | 68 | 149 | 60 mg of propofol administered. Increased $ET_{Sevo}$ to1.8%. |
| 1743 | Tumor capsular hemorrhage controlled | 60 | 41 | 103 | 2 units of vasopressin and 1 mg midazolam administered. Decreased $ET_{Sevo}$ to 1%. |
| 1745 | Tumor excision | 68 | 43 | 103 | - |
| 1746-1855 | Post hemorrhage averages | 73 | 42 | 105 | Total of 5 units of vasopressin, and 1g of CaCl administered. |
| 1855 | At skin closure | 68 | 32 | 103 | - |
| | EBL 600 | | | | |
| | I/Os | | | | |
| | IN | LR 1,200 | NS 250 | FFP 591 | PLt 302 |
| | Total: 2,343 | | | | |
| | OUT | EBL 600 | Urine 1,800 (3 mg Bumex) | | |
| | Total: 2,400 | | | | |
| | NET: Neg 57 | | | | |
| | OR Time: 4 hours 19 minutes. | | | | |
| | Total Procedure Time: 3 hours 18 minutes. | | | | |

Abbreviations: EBL, estimated blood loss; $ET_{Sevo}$ end-tidal sevoflurane; FFP, fresh frozen plasma; HR, heart rate; LR,; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PLTS, platelets.

airway pressure overnight and transitioned high-flow nasal cannulae. Pulmonary artery pressures remained stable in the 50/30 mmHg range and the PAC was removed on hospital day 11 (postoperative day three). The patient did not have any episodes of hypotension while in the ICU after pheochromocytoma resection. Respiratory insufficiency resolved by hospital day 12 (postoperative day four) when the patient was transferred to the floor for routine post-surgical care. He was discharged on hospital day 20 (postoperative day 12) once his INR became therapeutic. He was discharged on essentially the same heart failure regimen with which he was admitted: riociguat, 2 mg three times daily, ambrisentan, 10 mg daily, eplerenone, 37.5 mg daily, metolazone, 2.5 mg daily, and bumetanide, 2 mg twice daily.

## Discussion

Pheochromocytoma resection in the setting of CTEPH and right heart failure is a clinically challenging scenario due to juxtaposed perioperative management considerations. Traditional preoperative management of pheochromocytoma with alpha-blockade and intravascular volume expansion may produce unique challenges in a patient with CTEPH and pulmonary edema-induced hypoxia requiring oxygen therapy. Perioperative pheochromocytoma management often involves vasodilatory and cardiac depressant medications that could be harmful to a patient with pre-existing CTEPH and RV dysfunction. Additionally, coagulopathy in the setting of CTEPH requiring therapeutic anticoagulation, APLs, and ITP pose particular perioperative challenges. A comprehensive discussion of the pathophysiology and perioperative management for pheochromocytoma resection and CTEPH is well beyond the scope of this article. Salient points for the perioperative management of each disease process will be examined. A discussion of the patient's specific perioperative management will follow.

Preoperative workup and optimization for pheochromocytoma resection consists of symptom evaluation, catecholamine level measurements, syndromic evaluation (presence of multiple endocrine neoplasia), cardiac evaluation consisting of echocardiography and electrocardiography, radiologic imaging, alpha- or calcium-channel blockade, and volume loading.[1,2] "The Roizen criteria" consisting of no in-hospital BP >160/90 mmHg for 24 hours before surgery, no orthostatic hypotension with BP <80/45 mmHg, no ST or T wave changes for one week before surgery, and no more than five premature ventricular contractions per minute and serve as titration parameters for medical management.[1,2,8] Adequate preoperative workup is intended to prevent catecholamine-induced perioperative complications including hypertensive crisis, cardiac arrhythmias, pulmonary edema, and cardiac ischemia.[1] Preoperative anxiolysis and H2 blockade can help mitigate preinduction catecholamine surge.[2,8] Invasive monitoring with a preinduction arterial line is essential for beat-to-beat hemodynamic monitoring given the potential for volatile pressure fluctuations during the intraoperative period secondary to tumor manipulation and surgical stimulation. IV induction agents and volatile anesthetics that directly or indirectly increase sympathetic tone should be avoided.[2] Similarly, neuromuscular blocking agents that institute vagolysis, histamine release, catecholamine release, or cause defasciculation should be used with caution.[2,9,10] TEE is of high utility in patients with a history of cardiac disease.[2] A variety of vasoactive agents can be used to manage rapid hemodynamic fluctuations caused by catecholamine surge. Traditionally, nitric oxide modulators, such as nitroprusside and nitroglycerin, have been employed to counter hypertensive crisis during pheochromocytoma resection.[2] Calcium-channel blockers, such as nicardipine and clevidipine, are alternatives to nitric oxide modulators and demonstrate less reduction in preload, less tachycardia, and do not exhibit rebound tachycardia or cause cyanide toxicity.[2,8] Beta-receptor antagonists such as esmolol can counter intraoperative tachycardia and tachyarrhythmias.

Postoperative care can be complicated by profound hypotension due to tumor resection, residual alpha-blockade, and intraoperative bleeding.[1,2] Postoperative hypoglycemia can occur due to insulin resurgence after reduction in catecholamine levels.[1,2,8]

Pulmonary artery endarterectomy is the treatment of choice for patients with CTEPH. According to international registries, 36% of patients are not candidates for pulmonary artery endarterectomy due to distal lesions or other contraindications, with balloon angioplasty as an alternative intervention.[4] Despite procedural intervention, lifelong anticoagulation usually is necessary.[4,5] Medical management can include a combination of diuretics, oxygen, phosphodiesterse-5 inhibitors, endothelin-receptor antagonists, prostanoids, and the guanylate cyclase stimulator riociguat depending on the severity of pHTN and degree of RV failure.[4,5,11] In general, preoperative medical management of CTEPH should be continued during the operative period with the exception of anticoagulation.[3] Perioperative management of pHTN consists of maintaining SVR, maintaining or improving RV contractility, and the reduction or maintenance of PVR.[3,6] Avoiding anxiety, pain, hypoxia, hypercarbia, acidosis, and hypothermia are keys to maintenance or reduction of pHTN.[3,6] PACs can be useful in managing pHTN in the perioperative setting by allowing for titration of pulmonary vasodilator therapy based on pulmonary artery pressures.[12] However, it should be noted that it is questionable as to whether this improves perioperative outcomes, as PAC data interpretation can be misleading and confounded by PEEP, vasopressors, and poor cardiac contractility.[2,13] In some studies, TEE use in patients with pHTN undergoing noncardiac surgery changed management 30%-to-50% of the time.[14] IV induction agents that significantly reduce SVR and RV contractility, such as propofol, should be carefully titrated. Administration in conjunction with vasopressors and other inotropic agents may be advisable.[3,14] Fluorinated volatile anesthetics cause depression of RV contractility, with sevoflurane having minimal effect on PVR.[2,3] Although nitrous oxide can have a more stable intraoperative hemodynamic profile compared with other inhaled volatile agents, it is known for increasing PVR.[14] Norepinephrine and phenylephrine are excellent agents to maintain SVR; however, higher doses of

both medications can cause an increase in PVR.[15] Vasopressin is an effective medication for maintenance of SVR in the setting of pHTN as it does little to increase PVR.[16-18] Epinephrine is an effective inotrope for RV failure in the setting of pHTN secondary to the ability to increase cardiac contractility and SVR. The inodilators dobutamine and milrinone can be used to augment cardiac contractility but may require additional vasoconstrictor support due to their propensity to decrease SVR.[2,3,14] PVR reduction can be achieved by using pulmonary vasodilators such as inhaled nitric oxide and prostacyclins. There is evidence that inhaled nitric oxide can improve ventilator-perfusion mismatch, even in patients with CTEPH, but definitive benefit has not been proven.[3,11,19] It should be noted that prostacyclins improve ventilator-perfusion mismatching but also can decrease SVR.[11,14] Postoperatively, the patient should be held to strict tracheal extubation criteria and continuation of inotropic support should be considered out of concern for respiratory failure leading to exacerbation of pHTN and fulminant RV failure.[3]

Perioperative management of a patient with CTEPH, pulmonary edema, RV failure, and idiopathic thrombocytopenia undergoing pheochromocytoma resection requires a careful balance of competing therapies. In the preoperative period, the patient required alpha-blockade and gentle volume loading. Clinically, the patient exhibited peripheral edema, two-pillow orthopnea, night oxygen requirement, and reduced activity tolerance that likely was indicative of CTEPH-induced pulmonary edema and RV failure. Echocardiography and right heart catheterization confirmed this. The authors chose to maintain the patient's current diuretic regimen in addition to mild volume loading. To monitor pulmonary artery pressures, a PAC was placed on admission. The authors' institution has a great deal of clinical experience with these catheters as they are placed regularly in cardiac surgical patients. Alpha-blockade was titrated to orthostasis while maintaining MAPs >70 mmHg to maintain RV perfusion due to mPAPs averaging in the 40-mmHg range. Preoperative anticoagulation was continued with argatroban because the authors felt the risk of additional clot burden exacerbating the patient's CTEPH leading to fulminant RV failure outweighed the increased risk of perioperative bleeding in the setting of thrombocytopenia. The patient responded well to IVIG infusions and platelet transfusions. No further workup or management was initiated.

Intraoperative monitoring with both TEE and PAC provided dual monitoring of RV function and pulmonary artery pressures in real time. The PAC helped distinguish RV failure due to pHTN versus other causes and accordingly, allowed tailoring of the management strategy. Intraoperatively, there was no discordance between CCO metrics and ventricular function seen on TEE. In fact, the patient's RV function on TEE was normal under general anesthesia. Perhaps an $F_IO_2$ of 1.0 significantly decreased his PVR allowing for optimized RV function. Presence of a clot on the PAC served as the only notable intraoperative echocardiographic finding. This clot likely formed while the patient was on systemic anticoagulation and thrombocytopenic, further illustrating the severity of the patient's APLS-induced coagulopathy despite normal thromboelastography. MAPs >70 mmHg were maintained to ensure adequate perfusion to the RV in the setting of pHTN. Vasopressin was used for episodes of hypotension in place of catecholamines due to the patient's alpha-blockade and vasopressin's limited effect on PVR.[16-18] Traditional antihypertensive agents used in pheochromocytoma resection, such as esmolol and nitroglycerin, were avoided due to concern for decreasing SVR and contractility in the setting of severe pHTN. Episodes of hypertension were treated with small boluses of propofol, fentanyl, and increasing the delivery of sevoflurane. Without question, an assortment of vasoactive medications could have been used due to the patient's adequate cardiac function seen on TEE and CCO. However, small boluses and adjustments of these medications allowed for immediate, easily reversible, and short-acting treatment of hypertensive crises with minimal effect on cardiac function and RV perfusion. Although an $F_IO_2$ of 1.0 may be detrimental, the authors maintained this throughout the case to mitigate any exacerbation in pHTN and to adequately oxygenate the patient in the setting of significant pulmonary edema.[3,6,20] Diuretics were given to treat pulmonary edema and improve oxygen exchange. No inhaled pulmonary vasodilators were administered, as expedient postoperative extubation was desired. The patient was left intubated due to a $PaO_2/F_IO_2$ ratio of 132 on an $F_IO_2$ of 1.0.

The patient was extubated on postoperative day one, with a TTE showing moderate RV dilation. This was attributed to increased mPAPs from lower $F_IO_2$ administration post-extubation in concert with intraoperative blood product and crystalloid loading. Home diuretics and pHTN medication regimens were restarted. The patient slowly was weaned off supplemental oxygen. The patient was bridged to warfarin using an argatroban infusion. The patient's postoperative course was uncomplicated and no episodes of hypertension, hypotension, or hypoglycemia occurred.

In conclusion, patients undergoing pheochromocytoma resection with CTEPH and idiopathic thrombocytopenia present with juxtaposing goals in perioperative management. Management of pHTN and RV failure should be of the utmost concern. Augmentation of RV function and mitigation of PVR should be balanced with the need to block catecholamine-induced sympathetic surge. Postoperatively, special attention should be paid to treating hypotension, hypoglycemia, and worsening RV failure due to operative fluid administration. Continuation with preoperative and postoperative anticoagulation should be a risk:benefit ratio decision, but anticoagulation remains advisable due to concern for untreated pulmonary artery clot burden.

## Expert Commentary*

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Pheochromocytomas and catecholamine-secreting paragangliomas are challenging tumors that inspire fear, dogma, debate, and, above all, careful coordination between specialist surgeons and anesthesiologists. Although it is unlikely that

definitive data will inform the best approach to resection, sound perioperative management principles have improved the treatment of patients that have them.

Paraganglioma refers to neuroendocrine neoplasm; most of these do not secrete catecholamines. When they do, they can progress to become symptomatic and life-threatening. Pheochromocytomas are secreting adrenal paragangliomas. These tumors are the most common catecholamine-secreting paragangliomas, and many refer to the entire group of catecholamine-secreting tumors under the general term "pheochromocytoma." They are typically slow-growing and occasionally cancerous. Most patients will present in the fifth and sixth decades of life. Surgical resection is the preferred treatment and most patients should be referred for advanced surgical and anesthetic care. Tumors are very rare. A recent review from the Netherlands suggested an incidence of 0.04 to 0.21 per 100,000 patient years.[21] The most typical clinical presentation is with hypertension. Patients may exhibit symptoms of sweating, headache, palpitations, anxiety, pallor, flushing, and trembling. Signs and symptoms aid the diagnosis, as not all patients will present with hypertension. Other findings include hyperglycemia and changes in activity tolerance.

Diagnosis involves biochemical and anatomic testing. The best marker for secreting paragangliomas is plasmafree metanephrines. A large cohort suggested a sensitivity of 99% and a specificity of 89% for the test.[22] Urinary total metanephrines (specificity 93%) and urinary vanillylmandelic acid (specificity 95%) are high-specificity tests with lesser sensitivities that may help confirm a diagnosis. Although the overwhelming majority of tumors are located in the adrenal glands, patients should be evaluated for extra-adrenal and metastatic disease to determine the best surgical approach. Of adrenal locations, anesthesiologists should be aware of the higher risk of large intraoperative blood loss with right-sided adrenal tumors, due to the shorter length of the right adrenal vein. Common problems associated with catecholamine-secreting tumors include cardiomyopathies and insulin intolerance. The former can be a chronic cardiomyopathy, either hypertrophic or dilated, or acute (Takotsubo's cardiomyopathy). Insulin intolerance typically is manifest by hyperglycemia, but patients may be at risk for hypoglycemia, especially after tumor resection.

The rareness of secreting paragangliomas is matched by the hazards of their removal. A need for specialist care is underscored by the high historic surgical mortality (3%-50%).[2] Correlates of higher morality in case series included preoperative systolic blood pressure, metanephrine level, and the number of recent surgeries.[23] Intraoperative cumulative catecholamine dose was another correlate with mortality.[24] These observations support an optimized and well-reasoned approach to surgical excision.

Most consensus opinion regarding perioperative care focuses on intensive preparation with agents that block or reduce the elevated catecholamine state and resection using minimally-invasive surgical techniques. Advances in both practices correlate with decreasing mortality.[25] The most common pharmacologic preparation is with alpha-blockade, targeting vasoconstrictive effects of the tumor. Potential advantages include reduction in hypertension and blunting episodes of intraoperative hypertension. Blockade may be helpful beyond simple effects on blood pressure. One physiologic study suggested an improvement in tissue oxygen delivery with alpha-blockade.[26] Other benefits of alpha-blockade may be important. It facilitates intravascular volume expansion that could improve intraoperative circulation, and retraining the vascular system might prevent postoperative vasoplegia and catecholamine dependence. For these reasons, guidelines recommend ten-to-14 days of alpha-blockade before surgery.[27] The most typical alpha-blocking agent is phenoxybenzamine. It is an irreversible inhibitor of the receptor, meaning it has the advantage of a long stable duration of action. Other competitive antagonists include terazosin, prazosin, and doxazosin, which may be more commonly available, but lack the smoother clinical profile of phenoxybenzamine. A starting dose for phenoxybenzamine is 10 mg orally twice a day, but the dose may be increased daily based on response. To optimize the preparation, titration of drugs to orthostatic BP is believed to maximize the physiologic effects of the preparation. Frequent, often daily communications with patients and regular orthostatic BP measurements, such as from sitting to standing, help establish the optimal dose of medications. Generally, higher doses will be tolerated more at night than during the day when patients are active. Patients can be encouraged to drink fluids and electrolytes as part of volume expansion. Classic criteria for preparation include no systolic BP $>160$ mmHg and no diastolic $>90$ mmHg for three or more days before surgery, minimal ectopic beats and no ST-segment changes on ECG.[28] Beta-blockade may have a role in preparation, but most recommend adding it only to control tachycardia. It is infrequently likely needed. Beta-blockade should not be started without alpha-blockade, as beta-2 antagonism could lead to worsened vasoconstriction.

Metirosine, a tyrosine hydroxylase inhibitor, blocks catecholamine synthesis, and is a novel option for the preparation for surgery. Although not commonly available and rarely used, its potential in directly countering the secretion of catecholamine secretion has been used successfully in pheochromocytoma preparation.

Consensus supporting preparation is not universal. In a large multicenter review involving 1,860 patients spanning 18 years, patients who were not blocked did not seem to suffer more complications or intraoperative derangements than patients who were blocked.[29] The unblocked subgroup was selected mostly from one center, and outcomes may not have included important postoperative complications. It is improbable that there ever will be a proper trial to address the controversy, but guidelines continue to support preoperative pharmacologic preparation.[27]

Anesthetic management of pheochromocytoma resection focuses on monitoring, access, something to lower the blood pressure, and something to raise it. Arterial BP monitoring, before induction, ensures rapid detection of changes in hemodynamics. Many patients will benefit from central venous access; in particular, to facilitate the delivery of vasoactive infusions. Tumor anatomy will inform decisions about large-bore venous access and any need to prepare blood products for

transfusion. TEE facilitates simultaneous assessment of cardiac filling and function, can help diagnose ischemia, and may be useful for some resections.

A vasodilator should be prepared to counteract episodes of vasoconstriction. Nitroglycerine and nitroprusside are both rapid- and short-acting agents that are easily titratable for potential brief hypotensive episodes. The former may be beneficial in facilitating intravascular volume loading by increasing venous capacitance. Although many cite the risks of cyanide toxicity with sodium nitroprusside, this complication is highly unlikely in the short period of surgery, and the major limitations to its use are availability and cost. Use of calcium-channel blockers is described, as is magnesium sulfate, which might also help prevent arrhythmias.

Unchecked vasodilators, including preoperative alpha-blockade, pronounced responses to vasodilators, hypovolemic shock from surgical hemorrhage, and a postoperative rebound vasoplegic state from catecholamine withdrawal are all potential causes of hypotension. Preparation of a vasoconstrictor is useful. Vasopression is a particularly useful agent, because it facilitates vasoconstriction independent of alpha-receptors and is effective in the setting of alpha-blockade. Similar benefit may exist for the administration of angiotensin II. Catecholamines may still be beneficial, but indirect agents such as ephedrine should be avoided. Similar concerns exist for ketamine, meperidine, droperidol, and morphine, the latter through histamine release. Succinylcholine may, through fasciculations, cause burst excretion of catecholamines from the tumor and lead to a hypertensive episode.

Periods of maximal risk during surgery include induction, incision, abdominal insufflation, tumor manipulation, and vascular isolation of the tumor. When the veins draining the tumor are ligated, hypotension may be significant. Careful coordination with the surgeon permits anticipation and a proactive approach. Increasing infused vasodilator dose and volume administration up to the point of ligation and then stopping the former is one approach to compensating for abrupt withdrawal of tumor catecholamine.

Phentolamine is a long-acting IV alpha-1 antagonist that may be useful for refractory cases of hypertension. Its long duration of action could contribute to post-excision hypotension. In the rare circumstance of discovery of an undiagnosed catecholamine-secreting tumor as an incidental finding during surgery, phentolamine might have a role in reducing hypertension, but should be tried after shorter-acting agents and magnesium sulfate have been considered.

Careful preparation and execution of a well-planned strategy mean that many pheochromocytoma excisions can proceed with little evidence of hemodynamic alterations. Under such conditions, the patient should be observed for signs of hypotension and hypoglycemia. Although adrenocortical insufficiency is a possibility, the presence of a functional contralateral adrenal gland makes it unlikely, but something to be considered if hypotension is persistent. Patients undergoing bilateral complete adrenalectomy with mineralocorticoid and glucocorticoid require steroid replacement and intensive postoperative monitoring. As catecholamines are short-acting hormones, the absence of hypotension or hypoglycemia in the first several hours after surgery suggests that the patient is unlikely to have further problems. Monitoring still is advised, but mandatory intensive care admission may not be necessary for these patients, especially with good pharmacologic preparation.[28]

Few cases are more emblematic of the advantages of coordinated perioperative care than the management of the resection of a catecholamine-secreting tumor. Advances in diagnosis and surgical techniques are the primary drivers of excellent perioperative outcomes, but the dedication and coordination of anesthesiologists remain the elements that makes these advances possible. Although many of the components of perioperative care have limited evidence to support them, the legacy of improvements and favorable outcomes argues strongly for a well-prepared approach to the surgery.

## Expert Commentary‡

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This is an interesting and complicated case of a patient with NF1 undergoing resection of a pheochromocytoma in the presence of several comorbidities including CTEPH and immune-mediated thrombocytopenia. The experienced anesthesia care team had to navigate between Scylla and Charybdis, resulting from the uncommon combination of disorders in this patient and the ensuing cardiovascular challenges.

Pheochromocytoma and sympathetic paragangliomas (PPGL) are catecholamine-producing and cetecholaimine-secreting neuroendocrine tumors derived from chromaffin tissue of the adrenal medulla and the extra-adrenal sympathetic paraganglia, respectively. Approximately 80%-to-85% of PPGL are pheochromocytomas, which may occur at almost any age, with a peak incidence between the fourth and sixth decade without predilection for a specific side or sex. PPGL are rare tumors, but their incidence has increased significantly over the past two decades.[21] The majority of new cases with PPGL are detected nowadays in the presymptomatic stage as a result of DNA mutation screening programs (5%-27%) and the widespread use of imaging techniques revealing PPGL as an incidental finding (36%-65%).

PPGL has the highest known heritability rate among all human tumors, and approximately 40% of all PPGL patients carry a germline mutation in one of the 25 susceptibility genes currently known.[30] NF1, also known as Recklinghausen's disease, is an autosomal dominant–transmitted disorder characterized by the development of neurofibromas and hyperpigmentation (café-au-lait macules, freckling). It has a prevalence of about one in 3000 live births. The occurrence of a pheochromocytoma in this patient is not just a coincidence, as NF1 is one of the several genetic disorders predisposing to the development of PPGL.

Of notice, an adrenal mass had been identified incidentally in this patient six years earlier by a computed tomography

scan. Each patient with an adrenal incidentaloma should be evaluated carefully for symptoms and signs of hormone overproduction or potential malignancy. This evaluation includes biochemical testing to search for overproduction of catecholamines (by measurement of metanephrines in plasma or 24-hour urine), cortisol, or aldosterone (only in case of hypertension). In general, up to 7% of all adrenal incidentalomas are unmasked as pheochromocytomas.[31] This risk is considerably higher when an adrenal incidentaloma is discovered in a patient with a genetic predisposition for PPGL like NF1. Apparently, endocrine evaluation with measurement of metanephrines was not performed in this patient at the time the adrenal mass initially was detected, which contributed to a considerable diagnostic delay.

The clinical presentation of PPGL is highly heterogeneous and no single symptom is pathognomonic. It is for this reason that the disorder is often designated as 'the great mimicker'. Hypertension commonly is regarded as a cardinal symptom but lacks discriminative power because of the high prevalence of hypertension in the general population.[32] Furthermore, approximately 5%-to-15% of PPGL patients are normotensive, and only a minority of patients will present with the classic triad of headache, sweating, and palpitations.[33]

Development of intestinal pseudo-obstruction is a less well-known yet potentially life-threatening complication of PPGL that produces a clinical picture suggestive of a mechanical intestinal obstruction in the absence of a demonstrable anatomic substrate. In retrospect, this most likely was the cause of the small bowel obstruction for which the patient had been treated in another hospital. Obviously, the 5-cm adrenal mass was much too small to account for any relevant intestinal obstruction. Intestinal pseudo-obstruction may occur as a direct consequence of catecholamine hypersecretion, which decreases gastrointestinal peristaltic activity through inhibition of parasympathetic acetylcholine release and stimulation of β2-adrenergic receptors. In addition, catecholamine-induced stimulation of the alpha-1 and alpha-2 adrenergic receptors causes vasoconstriction, which may result in intestinal ischemia and, ultimately, in ischemic colitis, necrosis, and intestinal perforation.[34] In the absence of clinical signs of intestinal ischemia, perforation, or toxic megacolon, the treatment of intestinal pseudo-obstruction in a patient with PPGL usually is conservative.

The only curative treatment for PPGL is surgical resection. As already mentioned, this is a high-risk procedure mainly due to the uncontrolled and massive release of catecholamines into the circulation that might be evoked during surgery in response to various mechanical (eg, endotracheal intubation, incision, peritoneal insufflation, tumor manipulation) and pharmacologic stimuli.[35] Major advances in radiology, medical management, anesthesiology, and surgery have contributed to the significant improvement in perioperative morbidity and mortality that has occurred in the past decades. For instance, current imaging techniques allow precise localization of the tumor that is essential for determining the optimal surgical approach. Longstanding excess of circulating catecholamines may have detrimental effects on the heart causing Takotsubo cardiomyopathy, myocardial infarction, acute heart failure, and arrhythmias. Such complications may develop irrespective of age, tumor size, or the presence of cardiovascular risk factors or symptoms. Thus, each patient planned for PPGL resection should be subjected to a thorough preoperative cardiac examination, including electrocardiogram, echocardiography, and a 24-hour ambulatory BP monitoring.

Another important aspect of the presurgical management is medical treatment to provide symptom relief and control of hypertension. For this purpose, alpha-adrenergic-receptor blockers often are considered as the treatment of choice. Either a selective (eg, doxasozin) or a non-selective (eg, phenoxybenzamine) alpha-adrenergic-receptor blocker may be given orally, preferably seven-to-14 days before surgery. Doxazosin has a shorter duration of action and causes less reflex tachycardia compared with phenoxybenzamine, and these characteristics made doxazosin probably the better choice for this patient. In a recently published randomized controlled trial, it was found that presurgical treatment with phenoxybenzamine resulted in less hemodynamic instability during PPGL surgery compared with doxasozin.[34] It could be argued whether administration of doxazosin in this normotensive patient really was indicated, in view of the congestive heart failure and a recent history of apparently uneventful invasive procedures. On the other hand, hemodynamic instability during PPGL surgery is also known to occur in normotensive patients.[36,37] It usually is recommended to consume a high sodium diet during treatment with an alpha-adrenergic-receptor blocker and to administer one-to-two liters of saline intravenously during the last 24 hours before surgery. The assumption underlying this recommendation is that a high-sodium diet and saline infusion reduce the risk of preoperative orthostatic hypotension and postoperative hypotension. There is, however, limited evidence to support this practice, which obviously is contraindicated in case of congestive heart failure.

Several investigators have questioned the need for presurgical treatment with alpha-adrenergic-receptor blockers.[29,38] It is worth mentioning here that there are no randomized placebo-controlled trials on this topic. In addition, the few available comparable studies that suggest that these drugs could be safely omitted are, without exception, small and retrospective in design and with several methodologic shortcomings. Based on their targeted mode of action and the longstanding clinical experience with these drugs, presurgical treatment with alpha-adrenergic-receptor blockers still is recommended by the Endocrine Society regardless of tumor size, degree of catecholamine production, or blood pressure.[30]

Instead of orally-administered alpha-adrenergic-receptor blockers, there are some alternatives that could have been considered in this particular case. As this patient was admitted to the ICU for optimal presurgical preparation under invasive monitoring with a pulmonary artery catheter, IV administration of a short-acting blood pressure–lowering agent might have been a good alternative. Frequently recommended IV agents are phentolamine, a competitive alpha-1 and alpha-2 adrenergic-receptor antagonist, and urapidil, a competitive alpha-1 adrenergic-receptor antagonist with a stimulating

effect on the central serotonin 5-$HT_{1a}$ receptor. Compared to phentolamine, urapidil does not cause reflex tachycardia and is, therefore, also suitable for patients with heart disease. Calcium-channel blockers such as oral nifedipine often are prescribed as an add-on drug to alpha-adrenergic-receptor blockers, yet also might be used as presurgical monotherapy in selected cases. These drugs inhibit the catecholamine-mediated calcium influx in vascular smooth muscle cells, thereby reducing the severity of catecholamine-mediated vasoconstriction, do not cause tachycardia, and only have a moderate effect on preload reduction. Among the calcium-channel blockers for IV administration, nicardipine or clevidipine have been most studied in this setting. In contrast to alpha-adrenergic-receptor blockers, calcium-channel blockers less frequently are associated with thrombocytopenia, which could have been an additional benefit in this specific clinical scenario. Finally, these rapid-acting antihypertensive drugs can be effectively combined with IV magnesium sulphate, a potent vasodilator that inhibits catecholamine release and also acts as a strong calcium antagonist. In addition, magnesium sulphate also has antiarrhythmic properties.

Advances in surgery have resulted over the years in a shift from PPGL resection through laparotomy to minimally-invasive procedures for small- to medium-sized pheochromocytomas (<6 cm), including laparoscopic transperitoneal, posterior retroperitoneal, and lateral retroperitoneal techniques. Compared to laparotomy, minimally-invasive techniques are associated with a shorter hospital stay and fewer complications, including less blood loss.[39] Hemorrhagic complications during laparoscopic adrenalectomies, however, still are not negligible, with a reported frequency of approximately 4%.[40] Unfortunately, the precautionary measures in this patient could not prevent the complication of adrenal hemorrhage and resultant hypotension during surgery. In addition to the coagulation disorders present in this patient, bleeding propensity probably also was increased by the co-existence of vascular fragility in patients with NF1.[41]

Undoubtedly, modernization of anesthetic techniques also has contributed to the significant reduction in perioperative complications of PPGL surgery in recent decades. Important measures are avoidance of certain drugs that might elicit uncontrolled catecholamine release, strict hemodynamic monitoring, and timely intervention to correct hypertension, hypotension, and cardiac arrhythmias. In addition to the standard monitoring systems recommended by the American Society of Anesthesiologists, pulmonary artery monitoring and TEE can be considered in patients with cardiac dysfunction to monitor volume status, ventricular diastolic filling (preload), contractility, and valvular function during the entire perioperative period, as also was done very nicely in this patient. The administration of propofol for induction and sevoflurane for maintenance anesthesia in this patient is a frequently used strategy. Other inhalation or IV anesthetic agents that have shown to be safe in case of PPGL surgery are isoflurane, enflurane, nitrous oxide, etomidate, and dexmedetomidine. Importantly, halothane, desflurane, ketamine, or thiopental should not be used, as these agents may sensitize the myocardium to circulating catecholamines and activate the sympathetic nervous system or stimulate catecholamine release indirectly through mast cell release of histamine. Neuromuscular blocking agents that can be used safely are vecuronium and rocuronium, which were used in this patient. Succinylcholine, pancuronium, atracurium, tobucurarine, mivacurium, and cisatracurium should be avoided, because these agents might precipitate a hypertensive crisis or severe cardiac arrhythmias due to their histamine-releasing properties. Fentanyl, remifentanil, alfentanil, or sufentanil can be used safely to achieve analgesia. The antiemetic prophylaxis was not described in this case yet it is worth mentioning that only ondansetron has been shown to be safe in patients not receiving alpha-adrenergic-receptor blockade. Importantly, the frequently prescribed metoclopramide and other dopamine-receptor antagonists are contraindicated without appropriate alpha-adrenergic-receptor blockade because these drugs might stimulate catecholamine release through activation of presynaptic dopamine D2-receptors. A comprehensive review of safe medications in patients with PPGL undergoing surgery recently was published.[35]

In conclusion, this case presentation highlighted the difficulties of perioperative PPGL management in the unique setting of a young patient with complicating comorbidities. It also underscored the importance of treating patients with these rare neuroendocrine tumors by specialized multidisciplinary teams in centers with broad expertise.

## References


1 Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. Lancet 2005;366:665–75.
2 Naranjo J, Dodd S, Martin Y. Perioperative management of pheochromocytoma. J Cardiothorac Vasc Anesth 2017;31:1427–39.
3 Aguirre MA, Lynch I, Hardman B. Perioperative management of pulmonary hypertension and right ventricular failure during noncardiac surgery. Adv Anesth 2018;36:201–30.
4 Pepke-Zaba J, Ghofrani HA, Hoeper MM. Medical management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26 :160107.
5 Rubin LJ, Hoeper MM, Klepetko W, et al. Current and future management of chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 2006;3:601–7.
6 Pritts CD, Pearl RG. Anesthesia for patients with pulmonary hypertension. Curr Opin Anaesthesiol 2010;23:411–6.
7 Van Wolferen SA, Marcus JT, Westerhof N, et al. Right coronary artery flow impairment in patients with pulmonary hypertension. Eur Heart J 2008;29:120–7.
8 Ramakrishna H. Pheochromocytoma resection: Current concepts in anesthetic management. J Anaesthesiol Clin Pharmacol 2015;31:317–23.
9 Kinney MA, Warner ME, vanHeerden JA, et al. Perianesthetic risks and outcomes of pheochromocytoma and paraganglioma resection. Anesth Analg 2000;91:1118–23.
10 Stoner TR Jr, Urbach KF. Cardiac arrhythmias associated with succinylchoine in a patient with pheochromocytoma. Anesthesiology 1968;29: 1228–9.
11 Strumpher J, Jacobsohn E. Pulmonary hypertension and right ventricular dysfunction: Physiology and perioperative management. J Cardiothorac Vasc Anesth 2011;25:687–704.
12 Minai OA, Yared JP, Kaw R, et al. Perioperative risk and management in patients with pulmonary hypertension. Chest 2013;144:329–40.
13 Cowie BS. Does the pulmonary artery catheter still have a role in the perioperative period? Anaesth Intensive Care 2011;39:345–55.

14 Pilkington SA, Taboada D, Martinez G. Pulmonary hypertension and its management in patients undergoing non-cardiac surgery. Anaesthesia 2015;70:56–70.
15 Price LC, Wort SJ, Finney SJ, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: A systematic literature review. Crit Care 2010;14:R169.
16 Siehr SL, Feinstein JA, Yang W, et al. Hemodynamic effects of phenylephrine, vasopressin, and epinephrine in children with pulmonary hypertension: A pilot study. Pediatr Crit Care Med 2016;17:428–37.
17 Currigan DA, Hughes RJ, Wright CE, et al. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: an in vitro study. Anesthesiology 2014;121:930–6.
18 Jeon Y1, Ryu JH, Lim YJ, et al. Comparative hemodynamic effects of vasopressin and norepinephrine after milrinone-induced hypotension in off-pump coronary artery bypass surgical patients. Eur J Cardiothorac Surg 2006;29:952–6.
19 Milger K, Felix JF, Voswinckel R, et al. Sildenafil versus nitric oxide for acute vasodilator testing in pulmonary arterial hypertension. Pulm Circ 2015;5:305–12.
20 Lumb AB, Walton LJ. Perioperative oxygen toxicity. Anesthesiol Clin 2012;30:591–605.
21 Berends AMA, Buitenwerf E, de Krijger RR, et al. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: A nationwide study and systematic review. Eur J Intern Med 2018;51:68–73.
22 Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: Which test is best? JAMA 2002;287:1427–34.
23 Plouin PF, Duclos JM, Soppelsa F, et al. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. J Clin Endocrinol Metab 2001;86:1480–6.
24 Gaujoux S, Bonnet S, Lentschener C, et al. Preoperative risk factors of hemodynamic instability during laparoscopic adrenalectomy for pheochromocytoma. Surg Endosc 2016;30:2984–93.
25 Livingstone M, Duttchen K, Thompson J, et al. Hemodynamic stability during pheochromocytoma resection: Lessons learned over the last two decades. Ann Surg Oncol 2015;22:4175–80.
26 Roizen MF, Hunt TK, Beaupre PN, et al. The effect of alpha-adrenergic blockade on cardiac performance and tissue oxygen delivery during excision of pheochromocytoma. Surgery 1983;94:941–5.
27 Chen H, Sippel RS, O'Dorisio MS, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas 2010;39:775–83.
28 Witteles RM, Kaplan EL, Roizen MF. Safe and cost-effective preoperative preparation of patients with pheochromocytoma. Anesth Analg 2000;91:302–4.
29 Groeben H, Walz MK, Nottebaum BJ, et al. International multicentre review of perioperative management and outcome for catecholamine-producing tumours. Br J Surg 2020;107:e170–8.
30 Lenders JWM, Kerstens MN, Amar L, et al. Genetics, diagnosis, management and future directions of research of phaeochromocytoma and paraganglioma: A position statement and consensus of the working group on endocrine hypertension of the European Society of Hypertension. J Hypertens 2020;38:1443–56.
31 Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European network for the study of adrenal tumors. Eur J Endocrinol 2016;175:G1–G34.
32 Omura M, Saito J, Yamaguchi K, et al. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. Hypertens Res 2004;27:193–202.
33 Geroula A, Deutschbein T, Langton K, et al. Pheochromocytoma and paraganglioma: Clincial feature-based disease probability in relation to catecholamine biochemistry and reason for disease suspicion. Eur J Endocrinol 2019;181:409–20.
34 Osinga TE, Kerstens MN, van der Klauw MM, et al. Intestinal pseudoobstruction as a complication of paragangliomas: Case report and literature review. Neth J Med 2013;71:512–7.
35 Berends AMA, Kerstens MN, Lenders JWM, et al. Approach to the patient: Perioperative management of the patient with pheochromocytoma or sympathetic paraganglioma. J Clin Endocrinol Metab 2020;105:dgaa441.
36 Scholten A, Vriens MR, Cromheecke GJ, et al. Hemodynamic instability during resection of pheochromocytoma in MEN versus non-MEN patients. Eur J Endocrinol 2011;165:91–6.
37 Lafont M, Fagour C, Haissaguerre M, et al. A. Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas. J Clin Endocrinol Metab 2015;100:417–21.
38 Buisset C, Guerin C, Cungi PJ, et al. Pheocromocytoma surgery without systematic preoperative pharmacological preparation: Insights from a referral tertiary center experience. Surg Endosc 2021;35:728–35.
39 Li J, Wang Y, Chang X, Han Z. Laparoscopic adrenalectomy (LA) vs open adrenalectomy (OA) for pheochromocytoma (PHEO): A systematic review and meta-analysis. Eur J Surg Oncol 2020;46:991–8.
40 Henry JF, Defechereux T, Raffaelli M, et al. Complications of laparoscopic adrenalectomy: Results of 169 consecutive procedures. World J Surg 2000;24:1342–6.
41 Rasko JE, North KN, Favaloro EJ, et al. Attenuated platelet sensitivity to collagen in patients with neurofibromatosis type 1. Br J Haematol 1995;89:582–8.