Perioperative Physiologic Pertubations of Pheochromocytoma: Opportunities for Integrated Pharmacologic Management of Systemic Vascular Resistance

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OBJECTIVES

After working through this problem-based learning discussion, the participant will:
- understand the perioperative utility of **echocardiography** in the management of pheochromocytoma;
- outline the goals of **preoperative preparation** in pheochromocytoma resection;
- appreciate the possibilities in **hemodynamic monitoring** for pheochromocytoma resection;
- understand the management options for a **hypertensive crisis** during resection of a pheochromocytoma;
- understand the management options for a **hypotensive crisis** during resection of a pheochromocytoma;
- appreciate the typical **postoperative considerations** in the management of pheochromocytoma.

STEM CASE - KEY QUESTIONS

A 47 year old man with no significant past medical history presented in respiratory distress to his local emergency room. His vital signs were:

P 166 beats/min, **BP** 212 / 155 mmHg, **RR** 45 breaths/min, **SpO2** 75 % (room air)

His EKG showed widespread ST segment depression and his CXR revealed pulmonary edema. After institution of mechanical ventilation and vasodilator therapy, he underwent cardiac catheterization. He had normal coronary arteries, and severly depressed ventricular function.

Question 1: Is an echocardiogram indicated? What additional information could it provide to guide clinical-decision-making of this presentation?

The patient was admitted to the ICU. His hypertension was initially controlled with nitroprusside and labetalol.

Question 2: What tests would you order to confirm the diagnosis of pheochromocytoma? What tests would you order to localize the tumor?

The diagnosis of pheochromocytoma is confirmed. The patient is scheduled for left adrenalectomy.

Question 3: What recommendations would you give to the critical care team for preoperative blood pressure control in this patient? What are the possible pharmacologic choices? Is there any concern with beta-blockade?

The preoperative hypertension is managed according to your recommendations. The patient improves clinically. Mechanical ventilation is successfully withdrawn.

Question 4: How would you evaluate the effectiveness of the preoperative antihypertensive regimen? When should the patient undergo surgery?

Question 5: Is a repeat echocardiogram indicated? What additional information could it provide to guide preoperative clinical-decision-making?

The patient presents for surgery. His vital signs are:

P 66 beats/min, **BP** 102 / 63 mmHg, **RR** 15 breaths/min, **SpO2** 94 % (room air)

Question 6: Is any invasive hemodynamic monitoring indicated? Is a pulmonary arterial catheter of any benefit? Would intraoperative echocardiography be indicated?

Question 7: What anesthetic technique would you choose? Is an epidural catheter of any benefit?

The patient is anesthetized. Surgical incision, and initial dissection are uneventful.

Question 8: What do you expect the intravascular volume status to be? How aggressively would you correct hypovolemia?

Question 9: When would you expect to see an intraoperative hypertensive crisis?

During dissection near the tumor, an acute hypertensive crisis develops with blood pressures of 220-250 / 125-150 mmHg.

Question 10: How would you manage this hemodynamic crisis? What intraoperative vasodilator therapy would you choose?

The surgical dissection is completed, and tumor resection begins. As the venous supply of the tumor is ligated, the blood pressure falls to 55 / 25 mmHg.

Question 11: What has happened to systemic vascular resistance? What are the possible reasons for this phenomenon?

Question 12: How would you pharmacologically correct the systemic vascular resistance?

The hemodynamics normalize, and the patient is transferred to the ICU after surgery.

Question 13: What do you expect to happen to systemic vascular resistance postoperatively? How would you address persistent hypertension? How would you address persistent hypotension?

PROBLEM BASED LEARNING DISCUSSION

Question 1: An echocardiogram would assess and document **cardiac function** at presentation. This patient has presented in hypertensive crisis and congestive cardaic failure. The extremely elevated systemic vascular resistance has caused ventricular dysfunction. An echocardiogram would not only assess **myocardial** performance, but would also interrogate **pericardial** and **endocardial** status for any associated pathology. Significant valvular disease would affect anesthetic management, and might require surgical intervention. Ventricular function, and regional wall motion motion could be quantified. Pericardial disease could be ruled out.

In this case, a transthoracic echocardiogram revealed an ejection fraction of 25%, global left ventricular hypokinesis, normal valvular function and a normal pericardium.

(***Echocardiographic case examples will be reviewed in the session***)

Question 2: The diagnosis of pheochromocytoma is first **confirmed** by demonstration of excessive circulating catecholamines and then the tumor is **localized** by radiological imaging. Serum measurements of normetanephrine and metanephrine, the catabolic products of norepinephrine and epinephrine, are often utilized to confirm the diagnosis of pheochromocytoma. . Computed tomography has a greater than 90% sensitivity for localization of pheochromocytoma. It must be remembered that pheochromocytoma is the **10% tumor**: 10% are extradrenal (including cardiac), 10% are bilateral, 10% are malignant, 10% are familial or part of the multiple endocrine neoplasia (MEN) syndromes.

In this case, the plasma free normetanephrine was 90 times normal, and the plasma free metanephrine was 70 times normal

In this case, computed tomography revealed a 10cm left adrenal mass.

Question 3: There are **two pharmacologic approaches** to preoperative control of pheochromocytoma: peripheral catecholamine blockade or decreasing tumor catecholamine synthesis. Preoperative **alpha-blockade** with **phenoxybenzamine** is an established gold-standard for preoperative catecholamine blockade in pheochromocytoma. Adequate alpha-blockade is evidenced by the **Roizen criteria**: a blood pressure less than 160/90 mmHg, orthostatic hypotension, ST segment resolution on EKG, and infrequent premature ventricular contractions. Phenoxybenxzamine is a non-selective and non-competitive alpha-blocker with a long half-life of greater than 24 hours. Aggressive intravascular volume expansion must accompany the induction of alpha-blockade, as profound hypovolemia is often unmasked by effective alpha-blockade. Phenoxybenzamine often induces reflex tachycardia, postoperative hyoptension, and postoperative somnolence. **Selective alpha1-blockade** of shorter duration would thus be advantageous to avoid this side-effect profile of phenoxybenzamine. Selective alpha1-blockade is possible with **doxazosin**, **prazosin** or **terazosin**. Doxazosin has a half -life of 12-24 hours that allows alpha-blockade comparable in efficacy with phenoxybenzamine. However, it is selective, and diasppears within 24 hours after pheochromocytoma resection. Prazosin and terazosin have half-lives of 3-6 hours, with even more favorable advantages, but they require more frequent dosing as well.

Beta-blockade, if required, should only be initiated in the presence of established alpha1-blockade. Beta2-stimulation causes peripheral vasodilation, and so **beta-blockade alone may precipitate a hypertensive crisis** from unopposed alpha1- stimulation from tumor catecholamines. Labetalol may still precipitate a hypertensive crisis, even though it is both an alpha-adrenergic and beta-adrenergic blocker.

Calcium channel blockade with nifedipine is a possible adjunctive therapy.

Decreasing tumor **catecholamine stores** with **methyltyrosine** offers an alternative to peripheral catecholamine blockade in preoperative preparation. Methyltyrosine inhibits tyrosine hydroxylase , the rate-limiting step in catecholamine synthesis. By decreasing tumor catecholamine stores, it most ideally approaches a **medical cure** for pheochromocytoma. In conjunction with alpha-blockade, it does faciltiate better perioperative hemodynamic control

In this case, preoperative catecholamine blockade was achieved with phenoxybenzamine and labetalol. The Roizen criteria were all met, except for occasional breakthrough hypertensive episodes.

Question 4: The patient's clinical status should be optimized before surgical intervention. The **Roizen criteria** provide a framework for judging the adequacy of preoperative catecholamine blockade. **End-organ insufficiency** such as myocardial or renal insufficiency should also have resolved. This is typically achieved in the setting of adequate catecholamine blockade and volume resuscitation.

In this case, the patient was euvolemic, normotensive, breathing room air and had a near normal effort tolerance. He still experienced episodes of breakthrough hypertension due to the very high serum norepinephrine levels induced by this very large tumor. After **extensive discussion**, the decision was to proceed with surgery, recognizing that perfect catecholamine blockade was probably unlikely in this setting due to tumor size and circulating catecholamine levels.

Question 5: Serial echocardiography **documents** recovery of ventricular function, as effective preoperative catecholamine blockade takes effect. **Adequate control of blood pressure does not always correlate with recovery of ventricular function**. The optimal timing of surgery should ideally include recovery of ventricular function. Thus, echocardiography is applicable throughout the preoperative process in pheochromocytoma: at presentation, during initiation of catecholamine blockade, and in deciding the timing of surgery.

In this case, repeat transthoracic echocardiography revealed normal left ventricular size and function.

(Echocardiographic case examples will be reviewed in the session)

Question 6: **Invasive arterial blood pressure monitoring** is essential, given the precipitous variations in systemic vascular resistance and pharmacologic intervention with potent vasodilator therapy. **Central venous access** is helpful for volume resuscitation, central venous pressure monitoring (CVP) and rapid administration of vasoactive agents. A **pulmonary arterial catheter** may be a useful adjunct, if left ventricular dysfunction is likely. Serial cardiac output

(CO)determination enables precise tracking of systemic vascular resistance (SVR = {[MAP - CVP] / **CO** X 80}, the key variable in the intraoperative management of pheochromocytoma. **Echocardiography** is particularly useful for hemodynamic rescue to guide circulatory resuscitation. In hemodynamic rescue, echocardiography allows rapid diagnosis and on-line therapy of **hypovolemia, myocardial insufficiency, and impaired systemic vascualr resistance.**

In this case, a radial arterial line and a pulmonary arterial catheter were placed after induction of anesthesia.

(Echocardiographic case examples will be reviewed in the session)

Question 7: General anesthesia is the more common technique, although there are **case reports** of successful regional anesthetics for pheochromocytoma resection. The key points are that the anesthesiologist chooses an anesthetic plan with which he/she is most **experienced**, and that close **communication** with the surgical team is maintained throughout the procedure. The skill with which the anesthetic is administered is more important than the anesthetic technique that is chosen. An epidural catheter allows preoperative opioid administration, intraoperative analgesia as well as effective postoperative pain management.

In this case, the anesthetic was a narcotic-based general anesthetic. A thoracic epidural catheter was placed preinduction, after adequate sedation. The epidural catheter was only employed for postoperative analgesia.

Question 8: The patient is typically **hypovolemic**. Aggressive **volume resuscitation** should be titrated to high normal central filling pressures and urine output of at leat 1cc/kg.hour. After tumor resection, additional volume resuscitation is required, given the precipitous fall in vascular tone due to massive acute catecholamine deficiency. Maintenance of perioperative euvolemia has been an important advance in the management of pheochromocytoma resection.

In this case, intravascular volume expansion maintained high normal central filling pressures and a urine output of greater than 1 cc/kg/hr. There was minimal blood loss (case totla was 300 cc).

Question 9: **Hypertensive crises** are typically due to acute **catecholamine excess**. Anesthetic depth should be adequate to blunt intraoperative stimulation from **intraoperative events** such as endotracheal intubation, surgical incision, surgical dissection and tumor manipulation. Anesthetic agents have also been associated with intraoperative hypertensive crisis: histamine release (morphine; atracurium); autonomic stimulation (succinylcholine; pancuronium); and sympathetic stimulation (meperidine; desflurane).

In this case, surgical anesthetic depth was maintained with a balanced anesthetic technique (fentanyl; isoflurane in oxygen). Neuromuscualr blockade was maintianed with titrated vecuronium, a neuromuscular blocker with minimal hemodynamic effects.

Question 10: There are **multiple vasodilator choices** for effective mangement of a hypertensive crisis: **inhalational** (sevoflurane; isoflurane); **alpha-blockers** (phentolamine); **beta-blockers** (esmolol; labetalol); **endothelial nitric oxide donors** (nitroglycerin; sodium nitroprusside); **calcium channel blockers** (nicardipine) and **dopamine1-agonists** (fenoldopam). The key to success is that the anesthesiologist again chooses a vasodilator regimen with which he/she is most **experienced**. The skill with which the vasodilator regimen is administered is more important than the specific vasodilators chosen.

In this case, the hypertensive crisis was managed with a balanced multimodal approach: **inhalational** (isoflurane) and **intravenous** (fentanyl; nicardipine; labetalol).

(The pharmacolgic rationale and profile for each class of agents will be discussed in the session)

Question 11: There is an **immediate massive acute catecholamine deficiency** as soon as the venous supply of the tumor is interrupted. Systemic vascular resistance falls and vasoplegia ensues. Residual vasomotor blockade from pre/intraoperative regimens further aggravates the vasoplegia. The vasogenic shock is further aggravated if residual hypovolemia is incorrected.

In this case, **immediate vasoplegia** on tumour isolation was expected due to the extremely high circulating levels of norepinephrine and epinephrine.

Question 12: The **response to vasoplegia** is to:

- discontinue all vasodilators (inhalational; intravenous);

- guarantee amnesia;

- ensure normovolemia; and,

- begin aggressive vasopressor support (phenylephrine; norepinephrine; epinephrine).

In this case, these steps did not normalize systemic vascular resistance, despite aggressive administration of norepinephrine and epinephrine. **Vasopressin** was added as a third vasopressor (**bolus of 10-20 units, infusion of 0.05 – 0.1 units/min**). This normalized vascular tone. This is a **novel application of vasopressin**; we have submitted this observation for publication.

(The pharmacolgic rationale and clinical applications of vasopressin will be discussed in the session)

Question 13: Persistent **postoperative hypotension**, as in this case, reflects persistent preoperative alpha-blockade, in the presence of normovolemia. **Persistent hypertension** is typically persists for a **week;** it is due to elevated catecholamine storesd in adrenergic nerve endings. Postoperative hypertension **beyond a week** suggests incomplete tumor resection or missed additional tumor elsewhere.

In this case, the patient had an uneventful postoperative course: tracheal exteubation was within 24 hours; vasopressor dependence lasted 36 hours; patient controlled epidural analgesia was begun 24 hours postoperatively. The patient was discharged from the ICU within 72 hours, and had a **complete recovery.**

Hemodynamic Formulae

Blood Pressure (BP) = Cardiac Output (CO) x Systemic Vascular Resistance (SVR)

CO = Heart Rate x Stroke Volume

Mean Arterial Pressure (MAP) = Diastolic Blood Pressure + 1/3 (Systolic Blood Pressure - Diastolic Blood Pressure)

SVR = {[MAP - CVP] / CO} X 80 (CVP = Central Venous Pressure)

PVR = {[MPAP - PAOP] / CO}X 80 (PAOP = Pulmonary Arterial Occlusion Pressure)

HEMODYNAMIC PROFILES			
Profile	Central Pressures	Cardiac Output	SVR
Hypovolemia	Low	Low	Normal-High
Pump Failure	High	Low	Normal-High
Low SVR	Normal-Low	Normal-High	Low
High PVR	High	Low	High

APPROACH TO HEMODYNAMIC MANAGEMENT

PUMP FAILURE		
Anatomic Level	Echo Finding	Clinical Decision
Pericardial	Fluid, Chamber Collapse	Drainage
Myocardial	Regional Wall Motion Abnormalities	Inotropes, Rule out ischemia, Possible mechanical support
Endocardial	Valvulopathy	Medical support, Possible surgical intervention

ECHO FOR HEMODYNAMIC RESCUE

ECHO IMAGING MODALITIES	
Imaging Modality	Clinical Application
Two Dimensional Imaging	Cardiac anatomy, measurements, regional wall motion analysis
Doppler Imaging	Blood velocity determinations, calculation of pressure gradients; valvular stenosis
Color Flow Doppler Imaging	Direction and amount of blood flow; valvular regurgitation; shunts

ECHO-CLINICAL CORRELATES

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LEARNING SUMMARY

This PBLD offers the participant the opportunity to explore pheochromocytoma and perioperative management of systemic vascular resistance. The newer modalities are emphasized e.g. novel alpha-blockers, echocardiography, and vasopressin. The balanced and integrated clinical management approach will emphasize hemodynamic rescue as a tool that is applicable throughout perioperative medicine. Detailed review of echocardiographic cases and specific pharmacologic agents will be available.