

# Anesthesia Considerations for Pheochromocytoma

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**Abstract**— The following review article in brief describes the definition, pathophysiology, management, preoperative assessment and perioperative anesthesia management in a case of pheochromocytoma.

**Keywords**— Anesthesia management; Pheochromocytoma.

## I. INTRODUCTION

**P**heochromocytomas are defined as catecholamine secreting tumors that arise from chromaffin cells of adrenal medulla in 90% of cases or sympathetic ganglia referred to as adrenal and extra adrenal pheochromocytoma or paraganglioma respectively. Paragangliomas can arise in the paravertebral sympathetic chain anywhere along the chain. 95% are localised to abdomen, and rest arise from thorax, urinary bladder, or neck, these can also be seen to be present in right atrium, broad ligament of ovary, or organ of Zuckerkandl. Pheochromocytomas can secrete both epinephrine and norepinephrine, however percentage of secreted norepinephrine is more than that secreted by normal glands. Pheochromocytomas are suspected when patients present with classical symptoms and suggest a family history and in some cases by an incidental finding of adrenal mass. Approximately 3% to 10% of adrenal “incidentalomas” prove to be pheochromocytomas.

History of Pheochromocytoma-(table I)

TABLE I. Important discoveries related to Pheochromocytoma.

Year	Scientist	Comments
1886	Felix Frankel	First made the description of a patient with pheochromocytoma
1912	Ludwig Pick (a pathologist)	Term pheochromocytoma was first coined by him.
1926	Cesar Roux and Charles Mayo	They were the first surgeons to successfully remove pheochromocytoma

### Adrenergic Receptors

#### 1) Alpha adrenergic receptors

- $\alpha_1$ - vasoconstriction, intestinal relaxation, uterine contraction, and pupillary dilatation.
- $\alpha_2$ - decreases presynaptic NE, platelet aggregation, vasoconstriction, decrease Insulin Release

#### 2) Beta Adrenergic receptors

- $\beta_1$ - Increase Heart rate/ contractility, Increase renin.
- $\beta_2$ - Vasodilatation, Bronchodilatation, Increase glycogenolysis and Increase gluconeogenesis
- $\beta_3$ -Increase lipolysis, Increase brown fat thermogenesis.

Effect of various agonist drugs on adrenergic receptors varies in several parameters. (Table II)

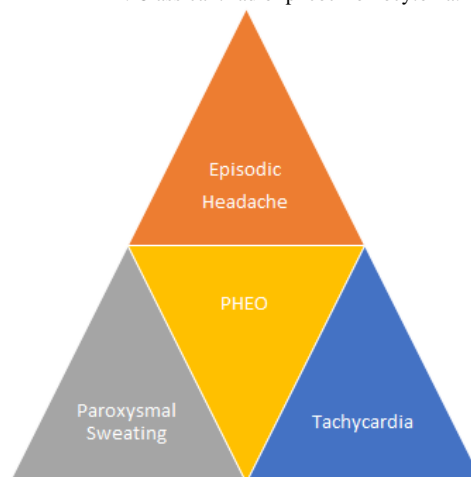
TABLE II. Effect of adrenergic agonist drugs.

DRUGS	HR	MAP	CO	PVR	BRONCHO-DILATION	RBF
Epinephrine	↑↑	↑	↑↑	↑/↓	↑↑	↓↓
Ephedrine	↑↑	↑↑	↑↑	↑	↑↑	↓↓
Nor epinephrine	↓	↑↑↑	↑/↓	↑↑	0	↓↓
Dopamine	↑↑	↑	↑↑↑	↑	0	↑↑↑
Dopexamine	↑↑↑↑	↑/↓	↑↑	↑	0	↑
Isoproterenol	↑↑↑	↓	↑↑↑	↓↓	↑↑↑	↑/↓
Dobutamine	↑	↑	↑↑↑	↓	0	↑

Pheochromocytoma presents with classic triad of symptoms:

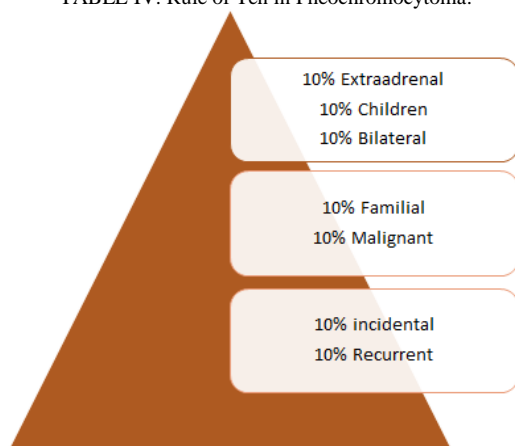
1. Headache which occur episodically
2. Sweating
3. Tachycardia

TABLE III. Classical triad of pheochromocytoma.



- ❖ Paroxysmal Hypertension is a classical sign of pheochromocytoma, however is non-specific for the disease. It is present in half of the patients, whereas most of the remaining patients have essential hypertension
- ❖ 5-10% of the patients have normal Blood pressure
- ❖ Headache is present in approximately 90% of symptomatic patients, however is variable in severity
- ❖ Sweating is present in 60-70% of patients

TABLE IV. Rule of Ten in Pheochromocytoma.



Effect of disease on different systems:

1. Cardio vascular system:
  - Depends on relative proportion of Epinephrine, Norepinephrine or Dopamine release. Majority secretes- Norepinephrine. Nausea and Vomiting are features of Dopamine secreting tumour.
  - Norepinephrine - Hypertension with bradycardia.
  - Epinephrine - systolic hypertension, diastolic hypotension, tachycardia, palpitations, dyspnea, weakness and panic attacks. Sometimes MI / Failure, Dilated Cardiomyopathy (because of excess catecholamines), polycythemia and orthostatic hypotension.
2. Central Nervous system :
  - Anxiety, Psychosis, Tremors, Hypertensive encephalopathy, Blurred vision and Psychiatric disorders
3. Metabolic disturbances :
  - Hyperglycemia, Hypermetabolism and weight loss, Polyuria and Polydipsia.
4. Suspicion of pheochromocytoma:
  - Hyper adrenergic spells (nonexertional palpitations, diaphoresis, headache, tremor, pallor), Hypertension that is difficult to control.
  - Familial syndrome that includes catecholamine secreting tumors (e.g., MEN 2, neurofibromatosis type 1, von Hippel–Lindau disease) (These individuals often have bilateral disease.)
  - Family history of pheochromocytoma with incidentally discovered adrenal mass.
  - Unusual BP response during anesthesia, surgery, or angiography.
  - Hypertension at a young age (e.g., <20 years old).
  - Idiopathic dilated cardiomyopathy. A history of gastric stromal tumor or pulmonary chondromas (Carney triad)

Complications:

Complications of pheochromocytoma are because of unopposed action of high blood pressure on critical organs

such as heart, brain and kidneys, and include Cerebrovascular accidents, acute kidney failure, acute respiratory distress, myocardial infarction, sudden heart attack and damage to nerves of eye.

Diagnosis is made as a combination of Clinical signs and symptoms, Biochemical tests and Radiological tests. (Table V)

Clinical diagnosis	By classical Signs and symptoms
Biochemical Tests- no single test is perfect 1. Free catecholamine levels in 24 hour urine 2. Plasma free metanephrine 3. Urinary metanephrine 4. Urinary VMA 5. Clonidine suppression test 6. Provocative tests	Familial  Urinary VMA is the oldest and inexpensive test Clonidine is a centrally acting $\alpha$ -2 agonist, which inhibits central neurogenic mediated catecholamine release but not catecholamine released autonomously by pheochromocytoma. Provocative tests (histamine, tyramine, Glucagon, metoclopramide and naloxone) used to stimulate catecholamine secretion from pheochromocytomas.
ECG:	Left ventricular hypertrophy and nonspecific T-wave changes are two of the more common ECG findings. Evidence of acute myocardial infarction or tachyarrhythmia.
Chest X ray	The chest radiograph may reveal cardiomegaly
Blood Count- CBC	Often shows an elevated hematocrit consistent with a reduced intravascular volume and hemoconcentration.
Radiological tests: a) MRI/CT – b) MIBG (Metaiodo benzyl guanidine)- c) Positron emission scans. d) Selective adrenal venous catheterisation and sampling. e) USG and MRI useful especially in pregnant patients. f) Arteriography must be performed with extreme care in these patients because a hypertensive crisis can be precipitated.	It is used in the non-invasive localization of these tumors. taken up by tumor , helpful in localizing recurrent tumor and extra- adrenal masses

Pre Operative Management

The reduction in perioperative mortality rates from a high of 45% to between 0% and 3% with the excision of pheochromocytoma is attributed to the introduction of  $\alpha$ -antagonists for preoperative therapy. However many drugs can be employed for adequate BP optimisation before surgery.

1. Perioperative blood pressure fluctuations, myocardial infarction, congestive heart failure, cardiac dysrhythmias, and cerebral haemorrhage all appear to be reduced in frequency when the patient has been treated before surgery with alpha blockers and the intravascular fluid compartment has been re-expanded.

2. Extended treatment with  $\alpha$ -antagonists is also effective in treating the clinical manifestations of catecholamine myocarditis.
3. All patients with pheochromocytoma must be managed with preoperative  $\alpha$ -adrenergic blockade at least 7 to 10 days before the surgical procedure, with the goal of normalizing BP and volume status.
4. Phenoxybenzamine is the preferred drug for preoperative preparation to control arterial BP and arrhythmias.
  - Phenoxybenzamine is an irreversible non-specific long acting alpha adrenergic blocking drug
  - Initial dosage is 10 mg OD or BD, and is increased by 10-20 mg every 48-72 hours to control blood pressure
  - Most patients are controlled with 20-100 mg of phenoxybenzamine
  - Blood pressure is measured two times in a day with patient lying, sitting and standing
  - Target blood pressure is less than 120/80 mmHg and SBP <90mmHg while standing
  - Patients should be told about common side effects such as fatigability, orthostatic hypotension and nasal congestion
5. Selective  $\alpha$ 1-adrenergic blocking agents (e.g., prazosin, terazosin, doxazosin) are preferable to phenoxybenzamine when long-term pharmacologic treatment is indicated (e.g., metastatic pheochromocytoma) because of the favourable side effect profiles of these drugs. The disadvantage of using these agents preoperatively is their incomplete degree of  $\alpha$ -adrenergic blockade, thus resulting in more episodes of intraoperative hypertension. Preoperative preparation with phenoxybenzamine is associated with more post-resection hypotension than is preparation with selective  $\alpha$ 1-adrenergic blocking agents.
6. After adequate  $\alpha$ -adrenergic blockade is achieved,  $\beta$ -adrenergic blockade may be started cautiously with short-acting drugs.
  - After 24 to 48 hours, if the patient tolerates  $\beta$ -adrenergic blockade, a long-acting preparation (e.g., metoprolol, atenolol) can be substituted.
  - The dose is then adjusted to control tachycardia with an HR goal of 60 to 80 beats/minute.
7. Others:
  - $\beta$ -Adrenergic blockade should never be initiated before  $\alpha$ -adrenergic blockade because blockade of vasodilatory peripheral  $\beta$ -adrenergic receptors with unopposed  $\alpha$ -Adrenergic receptor stimulation can lead to a further elevation in BP.
  - Clonidine, dexmedetomidine, and magnesium, have also been used to achieve suitable degrees of  $\alpha$ -adrenergic blockade preoperatively.
  - Perioperative  $\alpha$ -adrenergic blockade is most commonly used, another option involves the administration of a calcium channel blocker. Nicardipine is the most commonly used calcium channel blocker for pheochromocytoma management. The main role for calcium channel blockers is likely to supplement  $\alpha$ - and  $\beta$ -adrenergic blockade when BP control is inadequate or in patients with intolerable side effects
  - Nicardipine inhibit catecholamine release by blocking calcium entry.
    - They are effective in controlling both hypertension and tachycardia, when used as a single agent or with  $\alpha$ -blockers.
    - The starting dose of the sustained release preparation is 30 mg orally twice a day.
- Patients with acute hypertensive crises require hospitalization and treatment with intravenous sodium nitroprusside, phentolamine, or nicardipine.
- Magnesium therapy has shown efficacy for the resection of pheochromocytoma or paraganglioma during pregnancy.
- Unrecognized pheochromocytoma during pregnancy may be life threatening to the mother and fetus. Although the safety of adrenergic-blocking agents during pregnancy has not been established, these agents probably improve fetal survival in pregnant patients with pheochromocytoma. The trend is to perform surgery during the first trimester or at the time of cesarean delivery. There is no reason to terminate an early pregnancy, but the patient should be aware of the risk of spontaneous abortion resulting from abdominal surgery to remove the tumor.

TABLE VI. Anti-hypertensive drugs.

Drug	Action	Pre Operative BP Control	Pressor Crisis	Comments
Phenoxybenzamine	Non-Selective alpha 1 antagonist	20-160 mg/day per oral	-	Long half-life may accumulate
Doxazosine	Selective alpha1 antagonist	1-8 mg/day po	-	First dose effect, syncope.
Propranolol	Non selective beta antagonist	40-480 mg/day in divided dosage	1-2 mg iv bolus	Should never be given alone without alpha blockade
Atenolol	Selective beta 1 antagonist	50-100 mg/day		Long acting, unchanged by renal
Esmolol			250-500 $\mu$ gm/min followed by infusion 25-250 $\mu$ gm/min	Half life 9 minutes
Labetolol	Alpha and beta antagonist	200-800 mg/day	10 mg iv bolus	Weak alpha blockade
SNP	Direct vasodilator		0.5-1.5 $\mu$ gm /kg/min initially, max 8 $\mu$ gm /kg/min	Powerful vasodilator, short acting
MgSO4	Direct vasodilator and membrane stabilizer		2-4g iv bolus, followed by 1-2 g/h	Potentiates NM blockade
Nicardapine	Calcium channel antagonist		1-2 $\mu$ gm /kg/min, max 7.5 $\mu$ gm /kg/min	
Alpha-methyltyrosine	Inhibits biosynthesis of catecholamine's	1-4 g/day		Suitable for patients not amenable to surgery, nephrotoxic.

### Rozen Criteria

The following criteria are reasonable for assessing the adequacy of treatment:

1. No in-hospital arterial blood pressure reading higher than 165/90 mm Hg should be evident for 48 hours preoperatively. Measure arterial blood pressure (at specified interval like every 5 min) for 1 hour in a stressful environment (Postanesthesia care unit). If no blood pressure reading is higher than 165/90 mm Hg, this criterion is considered satisfied.
2. Orthostatic hypotension is acceptable as long as arterial blood pressure when the patient is standing is not less than 80/45 mm Hg.
3. The ECG should be free of ST-T changes that are not permanent.
4. No more than one premature ventricular contraction (PVC) should occur every 5 minutes.

### Differential diagnosis

1. Anxiety disorders, including Benzodiazepine withdrawal syndrome
2. Paragangliomas
3. Von Hippel–Lindau Disease
4. Essential hypertension
5. Hyperthyroidism
6. Insulinoma
7. Mercury poisoning
8. Paroxysmal supraventricular tachycardia
9. Renovascular hypertension
10. Carcinoid

### Surgical approaches

The principles of adrenalectomy for pheochromocytoma are:

1. Complete tumor resection.
2. Minimal tumor manipulation in avoidance of tumor seeding and hypertensive crisis.
3. Control of vascular supply.
4. Adequate exposure to avoid other organ injury.
5. In MEN associated adrenal medullary disease, surgical options include bilateral adrenalectomy or cortical-sparing subtotal adrenalectomy for adrenal medullary hyperplasia.

Operative approaches for adrenalectomy include:

1. Open anterior transabdominal approach.
2. Open thoracoabdominal approach.
3. Open posterior or lateral retroperitoneal approach.
4. Lateral transabdominal laparoscopic approach.
5. Posterior retroperitoneal laparoscopic approach.

### Perioperative Anesthesia Management

Symptomatic patients continue to receive medical therapy until tachycardia, cardiac dysrhythmias, and paroxysmal elevations in blood pressure are well controlled. If it is not possible to initiate  $\alpha$ -blocking therapy before surgery, or if the patient has received less than 48 hours of intensive treatment, it may be necessary to infuse nitroprusside during the induction of anesthesia. A low-dose infusion is often initiated

in anticipation of the marked blood pressure elevations that can occur with laryngoscopy and surgical stimulation. Improvements in imaging now allow most patients with solitary tumors without evidence of metastases or local invasion to undergo a laparoscopic retroperitoneal approach. If the surgeon needs to assess for bilateral disease or the dissection is too difficult, then the procedure can be converted to an open one. During laparoscopic surgery, creation of the pneumoperitoneum may cause release of catecholamines and large changes in hemodynamics that can be controlled with a vasodilator.

*Intraoperative management: Understand pharmacology and physiology:*

Drugs that should be avoided include: Drugs that inhibit catecholamine uptake, drugs releasing histamine and that cause indirect increase in catecholamines. Drugs include droperidol, Morphine, Atracurium, Pancuronium, Ketamine, Ephedrine, Halothane, Cocaine, Metoclopramide, and Scoline.

1. Intraoperative Goals of management include:
  - Avoid manoeuvres/drugs causing catecholamine release
  - Maintain stability by short acting drugs
  - Maintain normovolemia
2. The time periods of instability in which we anticipate surges of blood pressure include:
  - Induction and intubation
  - Incision
  - Pneumoperitoneum
  - Exploration and manipulation
  - Ligation of venous drainage
3. Monitoring during anesthesia management of a case of pheochromocytoma include:
  - Electrocardiogram
  - Pulse oximeter
  - End tidal carbon dioxide
  - Temperature probe
  - Invasive lines (CVP/ Arterial)
  - Cardiac Output monitoring  $\pm$
  - Urinary catheter.

Anesthesia technique:

General Anaesthesia +/- Epidural (Low thoracic)

1. Avoid stress, Anxiety, Pain, Hypoxia, Hypercarbia and Drugs - mentioned earlier.
2. Blood glucose should be monitored closely
3. Maintain Normothermia.
4. Although there is no clear advantage to one anesthetic technique over another, drugs that are known to liberate histamine are avoided. Virtually all anesthetic drugs and techniques (including isoflurane, sevoflurane, sufentanil, remifentanil, and fentanyl) have been used with success. Because of the potential for ventricular irritability, halothane is not administered.
5. A potent sedative-hypnotic, in combination with an opioid analgesic, is used for induction. It is extremely important

- to achieve an adequate depth of anaesthesia before proceeding with laryngoscopy to minimize the sympathetic nervous system response to this maneuver. Painful or stressful events such as intubation often cause an exaggerated stress response in less than perfectly anesthetized patients who have pheochromocytoma. This response is caused by release of catecholamines from nerve endings that are “loaded” by the reuptake process.
6. Slight stresses may result in catecholamine levels of 200 to 2000 pg/mL in normal patients. For a patient with pheochromocytoma, even simple stress can lead to blood catecholamine levels of 2000 to 20,000 pg/mL. Infarction of a tumor, with release of products onto peritoneal surfaces, or surgical pressure causing release of products, can result in blood levels of 200,000 to 1,000,000 pg/mL—a situation that should be anticipated and avoided (ask for a temporary stay of surgery, if at all possible, while the rate of nitroprusside infusion is increased).
  7. Maintenance is provided with an opioid analgesic (fentanyl, sufentanil, Remifentanyl) and a potent inhalation agent (Isoflurane, sevoflurane).
  8. Acute hypertensive crises are treated with intravenous infusions of nitroprusside or phentolamine.
    - Phentolamine is a short-acting  $\alpha$ -adrenergic antagonist that may be given as an intravenous bolus (2 to 5 mg) or by continuous infusion.
    - Tachydysrhythmia can be controlled with intravenous boluses of propranolol (1-mg increments) or by a continuous infusion of the ultrashort-acting selective  $\beta_1$ - adrenergic antagonist esmolol.
    - The disadvantage of long-acting beta-blockers may be persistence of bradycardia and hypotension after the tumor is removed. Even esmolol may be problematic because there are cases of cardiac arrest after clamping of the venous drainage in patients on large doses of esmolol.
    - Almost every vasodilator has been tried and recommended as an adjuvant to control hypertension.
    - Magnesium sulfate given as an infusion with intermittent boluses has successfully controlled blood pressure.
    - Nicardipine, nitroglycerin, diltiazem, fenoldopam, and prostaglandin E1 have all been used. The reduction in blood pressure that may occur after ligation of the

tumor's venous supply can be dangerously abrupt and should be anticipated through close communication with the surgical team.

- Restitution of any intravascular fluid deficit is the initial therapy in this situation. After replenishment of the intravascular volume, if the patient remains hypotensive, phenylephrine is administered. After surgery, catecholamine levels return to normal over several days.
- Approximately 75% of patients become normotensive within 10 days.

#### *Problems in Post Operative Period*

##### A) Hypotension

- Drop in catecholamines
- Residual alpha blockade.
- Down regulation.
- Suppression of normal adrenal
- Hypovolemia from blood/ fluid loss.
- Myocardial dysfunction.
- TREATMENT: fluids, vasopressors, vasopressin, glucocorticoids (B/L adrenalectomy)

##### B) Very somnolent:

- Due to sudden removal of activating catecholamines.
- Rule out hypoglycemia.

##### C) Hypoglycemia:

- Decrease epinephrine.
- Increase plasma insulin
- No gluconeogenesis and glycogenolysis.
- Give glucose containing fluids and monitor blood glucose.

##### D) Persistent hypertension

- Residual/Renal ischemia/Essential HTN

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