

Anesthesia Review Session Conference: Anesthesia for Carcinoid/ Neuroendocrine Tumors (NETs) and Carcinoid Syndrome

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Disclosures

- None

Goals and Objectives

By the end of this session, participants should be able to:

- Define and understand the terms carcinoid tumor, carcinoid syndrome, carcinoid crisis, as well as its clinical presentation
- Define standard biochemical testing for Carcinoid Syndrome
- Understand and express the pre, intra, and post operative implications and management of carcinoid syndrome

References

- Excerpts from Miller's Anesthesia, Barash's Clinical Anesthesia
- UptoDate
- ITE Keywords
- Open Access Media and Articles

- Castillo J, Silvay G, Weiner M. Anesthetic management of patients with carcinoid syndrome and carcinoid heart disease: The Mount Sinai Algorithm. J Cardioth Vasc Anes 2018; 32: 1023-1031.
- Mancuso K, Kaye AD, Boudreaux et al. Carcinoid syndrome and perioperative anesthetic considerations. J Clin Anes 2011; 23: 329-341.
- Stoelting Anesthesia and Coexisting Disease, 8th Edition, Chapter 17.
- Fernandez-Robles C, Carr ZJ, Oprea AD. Endocrine emergencies in anesthesia. Curr Opin Anesthesiol 2021; 34: 326-334.
- Perioperative Care of the Cancer Patient, 1st Edition, Chapter 28.

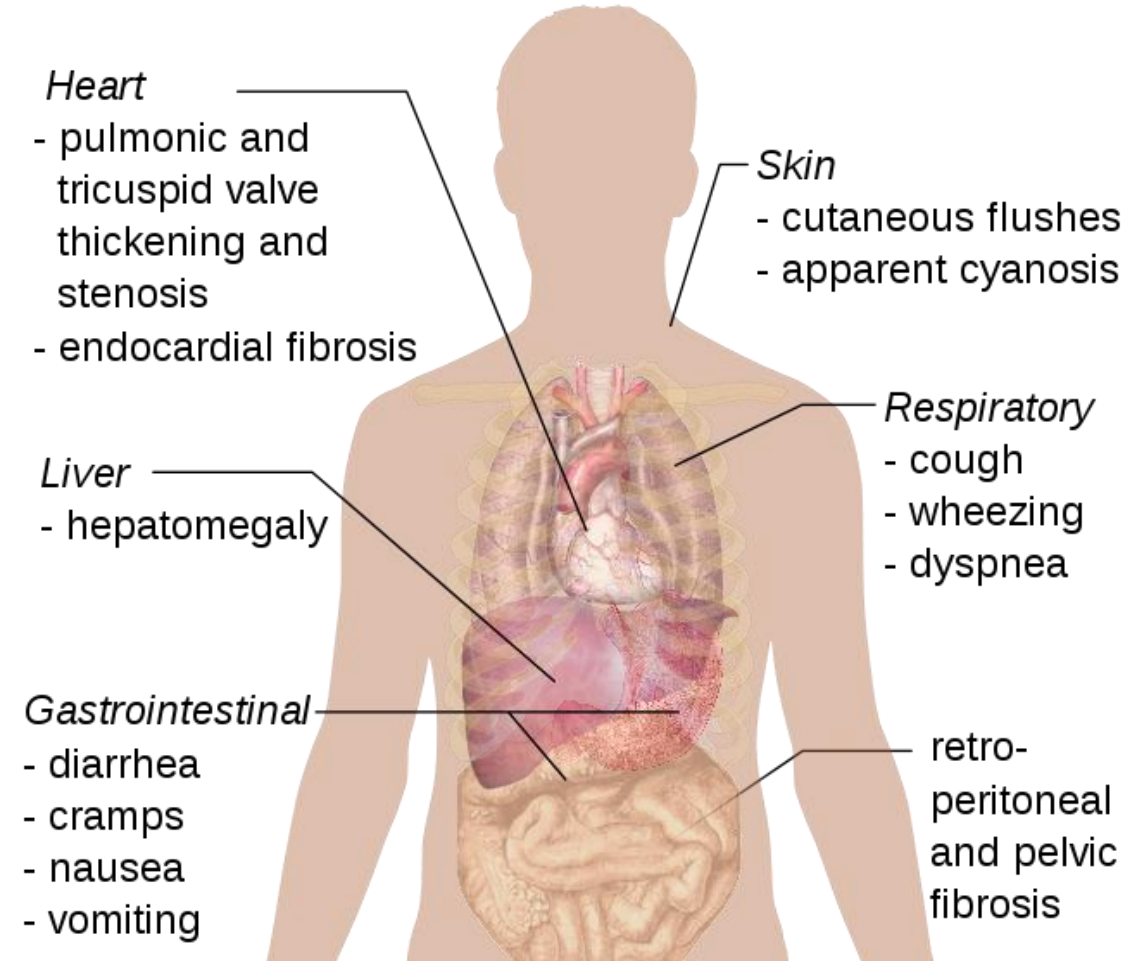
Carcinoid Tumors and Syndrome

- **Carcinoid Tumors** are rare neuroendocrine tumors (NETs) that can release mediators
- They are associated with MEN 1
- **Carcinoid Syndrome** is caused by:
 - Vasoactive amines (e.g., Serotonin, Norepinephrine, Histamine, Dopamine)
 - Polypeptides (e.g., Bradykinin, Somatostatin, VIP [vasoactive intestinal peptide], glucagon)
 - Prostaglandins
- Carcinoid syndrome can produce life-threatening perioperative hemodynamic instability
- The syndrome most often occurs with primary tumors that DO NOT drain in the portal system (eg. Bronchial, ovarian, or testicular tumors), or with hepatic metastases (the most common site of metastasis) because they bypass metabolism in the liver
- Also with large tumors, the liver's ability to inactivate these substances may be overwhelmed, resulting in the syndrome
- Most carcinoid tumors are located in the GI tract, most commonly the appendix, rectum, and ileum; however, they may also be found in the bronchial tree

Clinical manifestations

- Flushing, tachycardia, arrhythmias, diarrhea, malnutrition, wheezing, bronchospasm, and carcinoid heart disease
- Nonetheless most patients are **asymptomatic** because the liver inactivates the bioactive products of carcinoid tumors
- Signs and symptoms develop only when neuropeptides and amine substances are released in their active form into systemic circulation
- Consequently, patients with GI carcinoid tumors have manifestations of carcinoid syndrome only if they **bypass the portal system**

Carcinoid syndrome



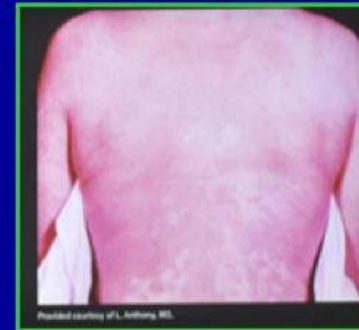
Carcinoid Heart Disease

- Characterized by endocardial fibrosis of the pulmonic and tricuspid valves.
- Can lead to tricuspid regurgitation, pulmonic stenosis, pulmonic regurgitation, right sided heart failure, peripheral edema, and hepatomegaly in affected individuals
- Can also lead to **Carcinoid Crisis**, which is associated with profound flushing, bronchospasm, tachycardia, and hemodynamic instability
- These life-threatening episodes can occur with **induction of anesthesia**, or other invasive procedures (e.g., tumor embolization)

Carcinoid Syndrome

- Caused by secretion of serotonin and other neuropeptides into systemic circulation
- Manifested by episodic flushing, diarrhea, and eventual right sided valvular heart disease
- Treated with somatostatin analogs

Flushing associated with carcinoid syndrome



Carcinoid Heart Disease: Tricuspid valve is fibrotic and leaflets retracted



Distinguishing Carcinoid from Cardiac Failure Symptoms

Table 19 Distinguishing Carcinoid from Cardiac Failure Symptoms

· Right Heart Failure	· Carcinoid Symptoms
· Dyspnea	· Flushing
· Fatigue	· Diarrhea
· Ascites	· Bronchospasm
· Anorexia	· Hypotension
· Edema	· Tachycardia

Biochemical Testing for Carcinoid Syndrome

Hormonal Markers

i. Blood Serotonin Concentration

- NOT recommended as standard diagnostic test, as the sensitivities and specificities are not well established
- Notably, false positive tests may occur due to release of platelet serotonin in stored blood samples, as well as from ingestion of tryptophan/serotonin rich foods

ii. Urinary excretion of 5-HIAA

- 5-HIAA (5-Hydroxyindolacetic acid), which is the end-product of serotonin metabolism
- Measure 24-hour urinary excretion of 5-HIAA
- **Preferred initial diagnostic test**, with sensitivity and specificity of over 90% for Carcinoid Syndrome respectively.
- Most useful in patients with **primary midgut** (jejunoileal, appendiceal, ascending colon) NETs as they produce the highest levels of serotonin
- Foregut (gastroduodenal, bronchus) and hindgut (transverse, descending, and sigmoid colon, rectum, genitourinary) NETs only rarely secrete serotonin

iii. Plasma 5-HIAA concentration

- Another reasonable option, especially for patients who have difficulty providing 24-hour urine specimens
- Reportedly correlate closely with urine 5-HIAA

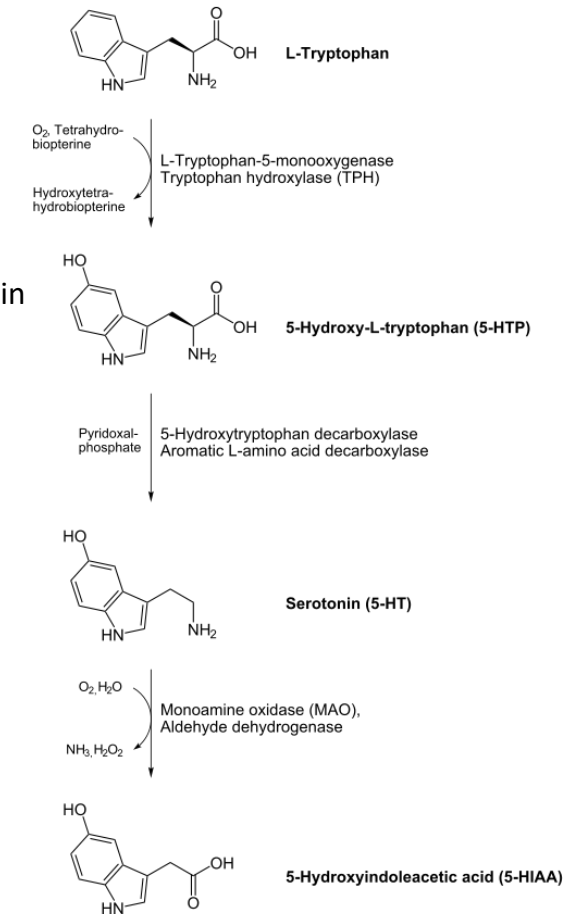
iv. Gastrin and VIP

- Some functional pancreatic NETs (notably gastrinomas and VIPomas) can be associated with severe diarrhea
- In such cases, 5-HIAA may be negative, but serum levels of gastrin and vasointestinal polypeptide (VIP) may be elevated, and aid in the **differential diagnosis**

Nonhormonal markers

i. Chromogranin A (CgA) concentration

- Chromogranins (designated A, B, and C) are proteins that are stored and released with peptides and amines in a variety of neuroendocrine tissues
- Due to its relatively low specificity, use of CgA as a screening test for diagnosis of a NET or carcinoid tumor is NOT recommended
- CgA may be an appropriate tumor biomarker for patients with an established diagnosis of advanced NET, in order to assess disease progression, response to therapy, or recurrence after surgical resection



Conditions associated with elevated chromogranin A

•Gastroenteropancreatic NETs

- Gastrointestinal tract (carcinoid tumors)
- Pancreatic NETs (islet cell tumors*)

•Endocrine disease

- Hyperparathyroidism
- Hyperthyroidism
- Pheochromocytoma
- Pituitary tumors
- Medullary thyroid carcinoma

•Gastrointestinal disorders

- Chronic atrophic gastritis
- Chronic hepatitis
- Colon cancer
- Hepatocellular carcinoma
- Inflammatory bowel disease
- Irritable bowel syndrome
- Liver cirrhosis
- Pancreatic adenocarcinoma
- Pancreatitis

•Cardiovascular disease

- Acute coronary syndrome
- Arterial hypertension
- Cardiac insufficiency/failure
- Essential hypertension
- Giant cell arteritis

•Drugs

- Proton pump inhibitors
- Histamine-2 receptor antagonists

•Inflammatory disease

- Airway obstruction in smokers
- Chronic bronchitis
- Systemic rheumatoid arthritis
- Systemic inflammatory response syndrome

•Renal disorders

- Renal insufficiency/failure

•Non-gastrointestinal cancers

- Breast cancer Ovarian cancer
- Prostate cancer (Even with a normal prostate-specific antigen [PSA] level.)
- Small cell lung cancer Neuroblastoma

•NETs: neuroendocrine tumors.

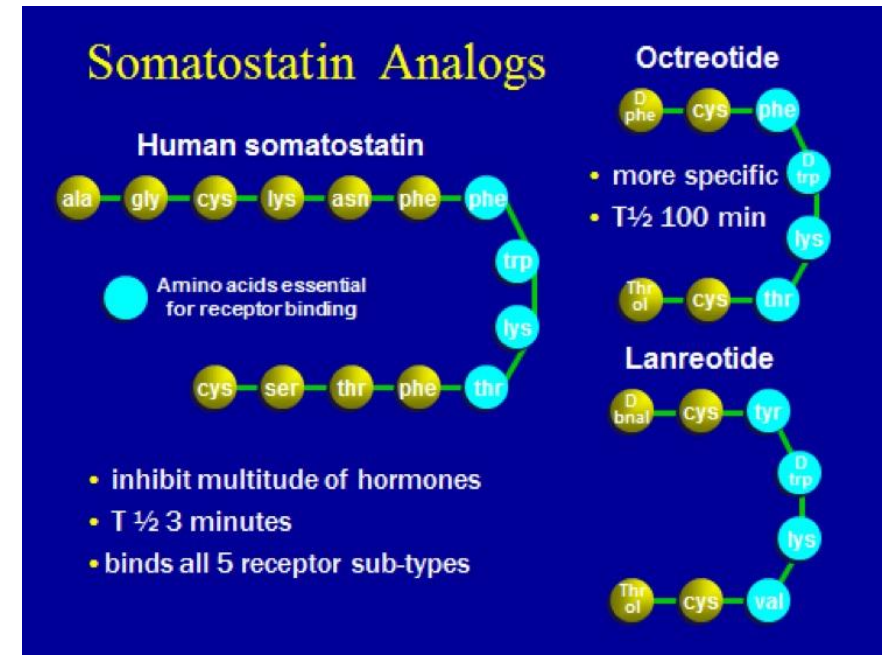
* e.g., gastrinomas, VIPomas, somatostatinomas, glucagonomas, nonfunctioning pancreatic NETs

Preoperative Evaluation

- The preoperative clinic evaluation should focus on dyspnea, orthopnea, wheezing, edema, arrhythmias, and murmurs
- Subsequent diagnostic tests are guided by the initial assessment
- Patients with chronic diarrhea need measurement of **electrolyte** and creatinine concentrations.
- Patients with **cardiac involvement** should have **ECG** and **echocardiogram**
- Malnourished patients should have an ECG, as a measurement of electrolyte and albumin concentrations
- Predictors of perioperative adverse events in these patients are:
 - Carcinoid heart disease
 - Elevated urine 5-hydroxyindolaetic acid (5-HIAA) concentrations
- The mainstay of pharmacologic treatment of carcinoid syndrome are **somatostatin analogues**, namely **Octreotide** and Lanreotide
- Preoperative treatment with octreotide (300-500 ug IV or subQ) helps mitigate the risks of intraoperative carcinoid crises
- An alternative approach for high-risk major procedures is to start a continuous IV 50 ug/hr infusion of octreotide for 12 hrs before surgery and continue it for at least 24-48 hours after surgery

Preoperative Management

- **Preoperative assessment** should include a history and physical exam that is focused on determining the presence and severity of any symptoms of carcinoid syndrome (eg. Flushing, diarrhea, bronchospasm, valvular heart disease)
- Presence of any triggering factors should also be determined
- For known cases of carcinoid tumor, imaging studies and specific laboratory tests should be performed prior to the scheduling of surgery
- Laboratory tests should include standard **chemistry, blood count, LFTs, blood glucose, an ECG,** and a **urinary 5-HIAA**
- Fluid and electrolyte abnormalities should be corrected, especially in patients with history of diarrhea
- **Preoperative therapy** is aimed at optimization of the patient for surgery and providing relief of symptoms. This may be achieved by antagonizing the mediators of carcinoid syndrome by blocking their release (**Octreotide** has become the mainstay of therapy)
 - **Octreotide** is a **synthetic analog of somatostatin** that is resistant to degradation by serum peptidases (thus has a longer half-life, 1.5 to 2 hours, when given subQ, and 50 minutes when given IV)
 - Octreotide **blocks hormonal release and inhibits the action of circulating peptides** by inhibiting either phosphatidylinositol or adenylate cyclase. Octreotide also **inhibits insulin secretion** in response to hyperglycemia. It has replaced nearly all other drugs as the drug of choice for treating carcinoid patients.
 - Various regimens for dosing octreotide have been reported. It has been suggested that subQ octreotide 100ug 3x daily be given for 2 weeks prior to surgery and 100 ug again before induction to prevent mediator release. Octreotide is also beneficial if it is given for only 24 hours prior to surgery.
 - If discontinued postoperatively, it should be weaned over the first week



Intraoperative Management

- Assess for control of symptoms on day of procedure, whether octreotide was needed to control symptoms, whether octreotide dosing up to date, whether octreotide should be administered intraoperatively (institutional variation).
- Consider **arterial line** monitoring for carcinoid tumor resection
 - Rapid changes in blood pressure can occur
 - Hypotension commonly seen with induction may trigger a **carcinoid crisis**
- Assess need for **large-bore peripheral intravenous access**, **central venous catheter**, **pulmonary artery catheter**, and **transesophageal echocardiography**:
 - **Abdominal carcinoids** often have rich vascular supply and metastases may involve the liver or other vessel-rich organs.
 - **Central venous catheter** may help in fluid management and medication administration.
 - For patients with **carcinoid heart disease**, a **pulmonary artery catheter** can allow monitoring of left ventricular function. For patients with right-sided cardiac involvement or undergoing cardiac surgery, **transesophageal echocardiography** can be beneficial.
- Maintain normothermia (hypothermia can trigger tumor mediator release)
- Propofol can be advantageous for induction, as it may suppress the sympathetic response to intubation.
- Avoid medications that may provoke tumor mediator release (such as succinylcholine and morphine; weigh risk/benefit with medications such as ephedrine, norepinephrine, and epinephrine).
- Regional anesthesia may be helpful in select cases for reducing the stress response to the surgical procedure.

Postoperative Management

- In addition to the standard goals of postoperative care, these patients must continue to be monitored carefully for signs of tumor mediator release (especially since they may have a delayed recovery from anesthesia)
- This may require placement in an ICU or acute care unit
- The effects of carcinoid tumor mediators may continue after tumor removal, and undetected metastases may still secrete peptides
- Fluids and electrolytes should be monitored since large fluid shifts may occur during some of these operations
- Analgesia to prevent excess sympathetic activity and stress is very important. IV fentanyl has been used with good results, as well as epidural analgesia

Perioperative Complications

- Complications may be associated with induction, intubation, or tumor manipulation; they can also occur at any time and without any provoking factor
- Early management is required to prevent progression to carcinoid crisis. **Cardiovascular instability** (usually presenting with BP and HR instability rather than rhythm abnormalities) is the most frequent complication but **bronchospasm**, **flushing**, and **hyperglycemia** have been reported.
- IV octreotide has become the treatment of choice, along with fluid administration, for hypotension in these patients
- If flushing occurs, it should be considered a warning sign of potential cardiovascular instability. Flushing typically responds to boluses of octreotide.
- Bronchospasm is less common than CV complications, BUT it may be severe and resistant to treatment. **Beta-agonists** may **exacerbate the problem** due to further tumor mediator release. Octreotide is especially useful for bronchospasm that is resistant to other treatments.
- Antihistamines as well as nebulized ipratropium have been used with good results.
- Hyperglycemia resulting from elevated serotonin levels should be monitored and treated, if necessary, with an insulin infusion

Summary

- **Carcinoid syndrome** may cause serious problems for an anesthesiologist due to the nature of variability of the clinical manifestations of the syndrome and the perioperative complications associated with it.
- **Urinary 5-HIAA** can provide a reliable indication of disease presence/ progression
- **Octreotide** has become the drug of choice in treating carcinoid patients
- Anesthetic technique should be focused on preventing carcinoid tumor mediator release from stress caused by the induction of anesthesia, endotracheal intubation, and tumor manipulation during the surgery
- **Invasive monitoring** may allow rapid detection of hemodynamic changes and should be considered, given cardiovascular instability (most often hypotension) is common and may be sudden and severe
- Successful anesthetic management of these patients often coincides with appropriate preoperative optimization of the patient

END