

"I have a NET... Why Focus upon the Heart? And What's a Cardiologist Doing on My Team, Anyway!"

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Caring4Noids



## Disclosure

Advisory board member (pertaining to Carcinoid Heart Disease) - Lexicon Pharmaceuticals, Inc -

## Today's Tour

- Epidemiology - incidence
- Etiology - cause
- Pathoanatomy - functional and anatomic manifestations of Carcinoid Heart Disease
- Treatment of Carcinoid Heart Disease
- Perioperative management – protecting the Carcinoid patient
- Timing of Procedures –to operate heart or tumor first ?
- Other Concerns – pertaining to the Carcinoid patient
- Brief Case Presentation – Final Exam
- What it all means to the Patient

## Epidemiology

- Incidence of **carcinoid cancer** ranges from 3-4 per 100,000 / year in USA
- Berge and Linell et al. showed an incidence of 8.4 per 100,000 / year in Sweden

Berge and Linell Acta Pathol Microbiol Scand A 1976;84(4):322-30

## Epidemiology

- At the time of diagnosis, 20-30% of the patients have **metastatic disease and carcinoid syndrome** with flushing (90%), diarrhea (70%), heart involvement (30%) and wheezing (15%)
- **Carcinoid Heart Disease (CHD)** may be the initial presentation of **carcinoid cancer** in as many as 20 % of patients and remains a major cause of morbidity and mortality

## Etiology of Carcinoid Heart Disease

Was described by Maria Spatz in 1964 based on research experience with **guinea pigs**

Experimental **carcinoid heart lesions** required 3 abnormalities or derangements:

- 1) Hepatic injury
- 2) Elevated serotonin level
- 3) Relative tryptophan deficiency (which results from the excessive production of serotonin)

**Treatment pearl:** Tryptophan deficiency is treated with **Niacin**.

## Pathoanatomy

- Serotonin...receptors...fibroblast proliferation (scarring)
- Severe fibrotic endocardial **pearly plaques** occur due to high serotonin levels
- Structural changes occur in valve leaflet architecture
- Mainly involving **right-sided** valves
- **Left-sided** involvement in the presence of a shunt, bronchial carcinoid tumor, or a very high serotonin level.

**Clinical Pearl:** We monitor **tumor markers:** urinary 5-HIAA, and blood Serotonin, Chromogranin-A, Pancreastatin and Neuron-specific enolase levels. (Goal: add bradykinin assay...more on this later)

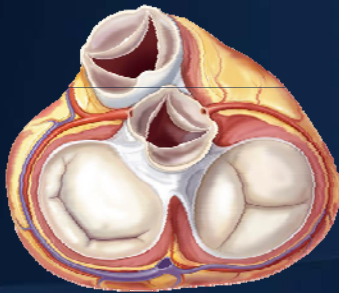
## Pathoanatomy

### In the Test Tube

- Fibroblasts + Serotonin → Fibroblast proliferation
- Addition of Omega III fish oil → Inhibits this effect

**Clinical Pearl:** Our Carcinoid patients are treated with Pro-Omega (purified / processed Omega III fish oil).

## L Pathoanatomy R 4 Valves (a transverse cut, looking down)



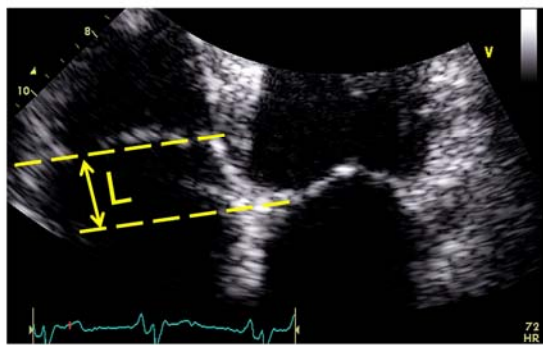
Echocardiographic image of normal Tricuspid and Mitral Valves

TV leaflet anatomy	Apical 4-chamber		Parasternal RV-inflow		Parasternal short-axis	
	Septal	Anterior	Septal	Anterior	Septal	Anterior
Septal	0%	100%	100%	0%	0%	48%
Anterior	100%	0%	0%	100%	0%	52%
Posterior	0%	0%	0%	0%	92%	0%

Anwar et al., 2007

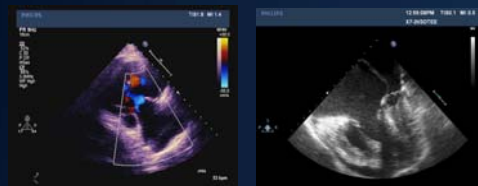
Echocardiographic Image of Normal Tricuspid Valve

AM Anwar et al., 2007

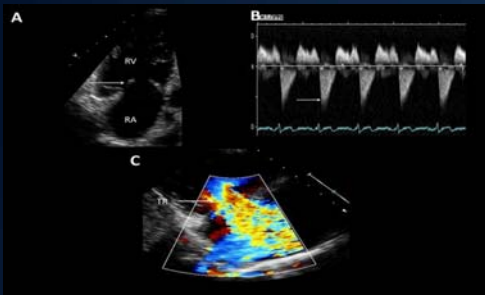


## Pathoanatomy

### Echocardiography of Tricuspid and Pulmonic Valves

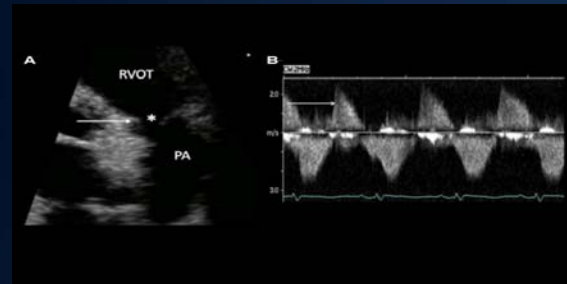


Echocardiographic image of Carcinoid Tricuspid Valve



WikiEcho.org

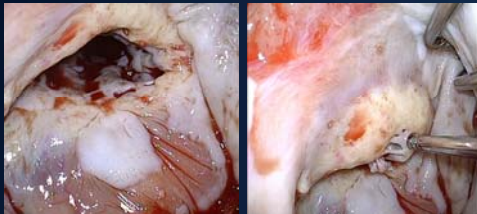
Echocardiographic image of Carcinoid Pulmonic Valve



WikiEcho.org

## Pathoanatomy

### Tricuspid Valvulopathy



Castillo et al. Rev Esp Cardiol. 2010 Jan;63(1):96

## Pathoanatomy

### CARCINOID TUMORS

"Functional" – Secretors → Carcinoid Syndrome

"Nonfunctional" – Nonsecretors → No Syndrome

CARCINOID SYNDROME – **Functional** tumor

### CARCINOID HEART DISEASE -

Occurs in **50%** of patients with Carcinoid Syndrome

**95%** do **not** have tumor in heart; **5%** have cardiac mets.

**Functional CARCINOID CANCER** releases vasoactive substances (including serotonin) which stimulates serotonin receptors resulting in fibroblast proliferation (scar formation) on the inner lining of the heart

## Pathoanatomy

### Somatostatin

An **Inhibitory** peptide hormone

6 somatostatin genes in vertebrates; only 1 in humans

**Somatostatin Receptors** (Facilitate **inhibition**)

5 SSTR's; **SSTR2**

### Somatostatin Analogues

Octreotide, Lanreotide, Pasireotide

### Serotonin

Secreted by Carcinoid tumors

Major contributor to carcinoid syndrome

Stimulates Serotonin Receptors in the heart

**Clinical Pearl:** Somatostatin analogues have affinity to SSTR2, suppressing NET growth by suppressing tumor growth factors and inhibiting tumor release of vasoactive substances, including Serotonin and bradykinin.

## Pathoanatomy

**CARCINOID SYNDROME** - Features of carcinoid tumors are caused by the release of pharmacologically active mediators, including 5-hydroxytryptamine (**Serotonin**), prostaglandins, **kinins (including bradykinin)**, substance P, gastrin, somatostatin, corticotropin and neuron-specific enolase into the peripheral circulation.

Flushing

Diarrhea

Wheezing

Carcinoid Heart Disease

### CARCINOID CRISIS

Flushing

Diarrhea

Wheezing

**Marked increase or decrease of BP**

**Clinical Pearl:** Octreotide and Soluocortef are mainstays of Crisis treatment.

## Pathoanatomy

### CARCINOID HEART DISEASE

Caused by high concentration of serotonin secreted by large burden of metastases in the **liver** (or by tumor in the **ovaries**)

#### RIGHT HEART (More common)

Tricuspid Valve  
Pulmonic Valve

#### LEFT HEART (Less common)

Mitral Valve  
Aortic Valve

Reason: **SEROTONIN IS INACTIVATED IN LUNGS**

## Pathoanatomy

### CARCINOID HEART DISEASE (Continued)

IF THERE IS **LEFT HEART INVOLVEMENT**, search for 3 possible causes:

- Hole in the heart
  - atrial septal defect
  - patent foramen ovale
- Carcinoid Tumor in Chest or Lungs
  - serotonin
  - mitral and aortic valves
- Extremely High Concentration of Serotonin

## Pathoanatomy

### CARCINOID HEART DISEASE (Continued)

**CONSEQUENCES OF RIGHT HEART FAILURE:**  
EDEMA, ASCITES, EFFUSIONS

EDEMA OF LEGS

ASCITES WITHIN ABDOMEN

Bowel Edema/Malabsorption  
Malnutrition (**cardiac cachexia**)

CONGESTION OF LIVER

Congestion – **high risk of bleeding** dictates the therapeutic sequence  
(**Fix the heart first**)

PLEURAL EFFUSIONS AROUND LUNGS

Causes **shortness of breath** (due to pulmonary edema and restriction of lung expansion).

## Treatment - Valve Surgery

### CARCINOID HEART DISEASE (CONTINUED)

SURGERY for Carcinoid Valve Disease:

Tricuspid and Pulmonic Valve Replacement

Prosthetic Valve Choice:

Mechanical (**Metal**)-**durable** but **need Coumadin**

Biologic (**Tissue**)-**less durable** but **do not need Coumadin**

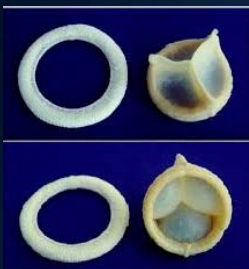
SEROTONIN LEVEL - **critical factor**

**46% recurrence of fibrosis with bioprosthetic valves**

**Telotristat could change this** (more on this later).

## Treatment - Prosthetic valves

### Bioprosthetic



### Mechanical



## Treatment - Other Cardiac Surgery

Close Interatrial **Defects**

atrial septal defect  
patent foramen ovale

Carcinoid **Tumor** in the Heart

chemotherapy trial preferable  
monitor with serial MRI or CT studies  
rarely requires surgical excision

## Treatment – Other Cardiac Surgical

- **Balloon Valvuloplasty** - occasionally, for isolated stenosis (but disease usually involves combined stenosis and insufficiency of more than one valve)
- **Transcatheter Valve replacement !**  
Pulmonic valve; IVC valve; SVC valve.  
bioprosthetic valves (therefore, susceptible to recurrent Carcinoid Valvulopathy)

(Karl Stangl – Charite, Univ of Berlin)

## Treatment - Other Surgery

### CARCINOID HEART DISEASE (Continued)

#### Other Cardiopulmonary Procedures:

##### Pacemakers

for Electrical Heart Blocks

prevent slow rhythm / fainting

##### Decortication of lung

for Scarring / Entrapment of Lung

alleviate shortness of breath

## Treatment - Medical

### CARCINOID HEART DISEASE (Continued)

#### MEDICAL THERAPY

Somatostatin analogues — inhibit tumor, reduce serotonin

Diuretics - remove fluid

Beta Blockers - slow the heart rate

ACE Inhibitors — vasodilators / lower blood pressure

Digoxin - strengthen contractility / control rhythm

Ketanserin - vasodilator; reduce pulmonary hypertension

**Experimental – Telotristat** - Most hopeful – 70-80% reduction of serotonin (greater reduction of serotonin than somatostatin analogues!)

## Treatment - Medical

### Manage Cardiovascular Risk Factors

**hypertension**

**hemoglobin A1C** (diabetic marker)

**lipid markers** (HDL, LDL, triglycerides)

**homocysteine**

**vitamins** (esp. B12, m-folic acid, D & K)

**physical activity / life style / diet**

**emotional state** (depression)

### Perioperative management can be life-saving!

#### Written instructions prior to cardiac cath, surgery, procedures

1. For prevention of a carcinoid crisis during and after surgery:
  - a. start an **octreotide** IV drip at 100 mcg/hour at least 2 hours pre-cath or pre-operatively and continue the drip throughout cath or surgery and in the ICU for 24-48 hours post-cath or post-operatively or until stable.
  - b. for signs or symptoms of a carcinoid crisis (flushing, diarrhea, wheezing and/or extreme increase or decrease of blood pressure) give an extra 100mcg bolus of **octreotide** IV and increase the drip to 200mcg/hr.
  - c. for persistence or recurrence of a crisis, give a repeat bolus of **octreotide** 100mcg IV and increase the drip to 300mcg/hr; repeat IV boluses and increase the drip by 100mcg/hr increments as often as necessary  
(We have used doses as high as 500mcg/hr without significant adverse effects; others have used even higher doses).
2. To inhibit tumor release of bradykinin, give 100mg **Solucortef** IV on call to the cath lab or the OR.
3. I remain available by telephone during the time of surgery and postoperatively 24/7.

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### Timing of Procedures

- Timing of procedures is critical
- In the **absence of right heart failure**, abdominal tumor-reductive procedures can proceed
- In the **presence of right heart failure**, **FIX THE HEART FIRST**, then reduce tumor burden and serotonin levels
- Often, right heart failure is advanced when the patient is first seen by a cardiologist!

### Other Concerns

Other effects of Cancer and Therapy upon the Heart

#### ANTITUMOR DRUGS

ADRIAMYCIN - heart failure

Monitor with Serial Echocardiograms

#### MONOCLONAL ANTIBODIES

Can adversely affect cardiac function

### Other Concerns

OTHER EFFECTS OF CANCER UPON THE HEART

NUTRITIONAL RISK – diminished appetite

Heart Failure → ascites / bowel edema

→ Malnutrition (Cardiac Cachexia)

### Other Concerns

#### CAUSES OF HEART FAILURE

HYPERTENSION (Stage I Heart Failure)

NONCARCINOID VALVULAR HEART DISEASE

Caution: Hypertension + valvular disease = increased risk of heart failure

### Other Concerns

#### OTHER CAUSES OF HEART FAILURE

##### CORONARY HEART DISEASE

Myocardial Infarction - scar

Global ischemia (severe diffuse coronary disease)

##### CONGENITAL HEART DISEASE

Hypertrophy - thickened cardiac walls

Infiltrative Diseases

Endocardial Diseases

(Loss of compliance / decreased contraction)

Anatomic and valvular anomalies

### Other Concerns

#### HEART FAILURE SYMPTOMS

##### LEFT HEART FAILURE SYMPTOMS

SHORTNESS OF BREATH

CHEST TIGHTNESS

PALPITATIONS

##### RIGHT HEART FAILURE SYMPTOMS / SIGNS

EXERTIONAL FATIGUE

LIVER PAIN / ASCITES

LOWER EXTREMITY EDEMA

### Other Concerns

#### PREVENT / TREAT HEART FAILURE

##### Control Blood Pressure

Vasodilators – preferred

Beta Blockers -- preferred

Diuretics -- often needed

Repair or Replace Diseased Left Heart Valves

Repair or Replace Diseased Right Heart Valves

Prevent progressive endocardial scarring

Somatostatin analogues

Telotristat – more promising!

## Other Concerns

PREVENT / TREAT HEART FAILURE – cont'd

TREAT RIGHT HEART FAILURE

Treat Left Heart Failure

Treat Reversible Pulmonary Disease

Treat chronic pulmonary embolism / Pulmonary hypertension / vasoconstriction

R/O deep vein thrombosis (blood clots)

Anticoagulation

Vasodilator therapy

Inferior Vena Cava filter

## Brief Case Presentation – Final Exam

Typical referral – phone call from Dick Warner

- 62 yo male
- 6 yr History of **diarrhea** – Rx'd as Irritable Bowel Syndrome
- 2 yr Hx of **flushing** and occasional **mid-abdom pain**
- Abdominal CT recently revealed **5 liver nodules**, a mesenteric **mass** with **spiculated calcified pattern**, **ascites** and bilateral **pleural effusions**
- Physical examination: **JVD with prominent V-waves**, systolic **murmurs**, a firm **pulsatile liver** edge with **HJR**, and **edema** up to the lower ribs.
- EGD and Colonoscopy **failed to reveal a primary tumor**
- Very high urinary 5-HIAA, and blood markers (Serotonin, Chromogranin A and Pancreastatin levels).

• **What we know** before we've met the patient: (explain)

**Clinical pearl:** resection of the primary tumor results in prolonged survival.

## WHAT IT ALL MEANS TO THE PATIENT

KNOWLEDGE of

HOW CANCER AFFECTS ONES HEART and  
HOW ONES HEART AFFECTS ONES CANCER

EMPOWERS US TO DO SOMETHING

**Team Approach** to the cancer patient

**No one person** can cover all the bases!

The patient is the most important team member.

The patient is involved in **all** decisions.

Collaboration among team is critical.

Focus on the **PATIENT**

Main Ingredients = **Courage / Persistence**

## WHAT IT ALL MEANS TO THE PATIENT II

**REWARDS** of Repairing the Heart

Eliminates Heart Failure thereby enabling Safe abdominal Tumor-reducing Surgery

Eliminates edema, ascites and pleural effusions – improves mobility, cures malnutrition, eliminates shortness of breath.

## WHAT IT ALL MEANS TO THE PATIENT V

**REWARDS** of CV RISK REDUCTION

Repairing Body / Fighting Cancer with

**greater Margin of Safety.**

Reasonable and Prudent to **Tune the Heart while Targeting Cancer.**

## Summary

**The management of patients with Carcinoid Heart Disease is focused upon**

- Accurately defining the pathoanatomy
- Aggressively managing heart failure
- Enlisting the active participation of patient and family
- Creating the proper medical / surgical / family **team**
- Protecting the patient from Carcinoid Crisis
- Prioritizing procedures
- Treating the **whole patient**
- Preventing recurrent valvulopathy
- Transitioning the patient to their next phase of anti-tumor treatment.

## Carcinoid Heart Disease Perioperative management

Thank you...and I wish to thank my colleagues at Mount Sinai's **Center for Carcinoid and Neuroendocrine Tumors** who, as do I, feel so strongly that a **team approach** is the formula for success.

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- Additional slides for questions

## Perioperative management

### 2 - Start treating right heart failure

(keep in mind patient may have > 25 Kg excess fluid due to right heart failure)

Worship the Scale – not the I/O data: **daily weight**

Portable Arm-cuff BP Machine: **sitting and standing**

Selection of diuretic regimen – **home treatment.**

**Daily AM phone call** to me/adjustment of medications

**Blood tests - weekly**

Follow-up exam at our office - **Q 2 weeks.**

**Avoid thoracentesis and paracentesis except in instances of significant patient discomfort!**



### Perioperative management

#### 3 - Decision re TPN – Could delay surgery

Estimated Dry Weight / Serum albumin  
Decision re home vs hospital TPN.

#### 4 - Referral for surgical consultations (CT and Onc)

**Prioritize procedures** – which procedure is performed first depends upon IVC pressure (in our case - fix the heart first)

#### 5 - Review of all data with team members

NET Expert, Surgical Oncologist, Cardiac Surgeon

#### 6 - Arrange Admission for Cardiac Cath/Surgery

Selection of prosthetic valve – Tissue vs Mechanical (Heidi Connally's experience with this issue is invaluable)  
Telotrastat on the horizon – this could change our choice of valves

### Perioperative management

#### 7 – The Protocol for Protection through Cardiac Cath and Surgery includes:

Solucortef – inhibits release of bradykinin  
Octreotide Drip -

Rodney Pommier et al published article – 2013 - entitled "Octreotide LAR and Bolus Octreotide Are Insufficient for Preventing Intraoperative Complications in Carcinoid Patients"

And we await a follow-up from his group when he reports more on this topic.

KRISTEN MASSIMINO, MD, OLA HARRSKOG, MD, SUELLEN POMMIER, PHD, AND RODNEY POMMIER, MD  
Journal of Surgical Oncology 2013;107:842–846

### Perioperative management

#### 8 - Instructions/warning for Surgeon, Anesthesiologist, Intensivist and Cath team–

- Continuous Octreotide Drip throughout
- Octreotide bolus and increase drip prn signs/symptoms of **carcinoid crisis**/ I Define crisis for the team
- Avoid **adrenergic pressors** – treat hypotension with fluids, Solucortef and octreotide
- Avoid **anesthetics** which stimulate an adrenergic response
- Avoid **analgesics** which stimulate an adrenergic response

### Perioperative management Instructions/warning

In a 1987 Case report

Larry Kvols and colleagues demonstrated the reversal of carcinoid crisis (with shock, and severe vasoconstriction following adrenergic pressors) within **40 seconds** of two 50mcg IV doses of a somatostatin analog (which was considered experimental at that time).

Carcinoid Crisis during Anesthesia: Successful Treatment With a Somatostatin Analogue\*. MARSH, H. MICHAEL M.B., B.S.; MARTIN, J. KIRK JR. M.D.; **KVOLS, LARRY K. M.D.**; GRACEY, DOUGLAS R. M.D.; WARNER, MARK A. M.D.; WARNER, MARY E. M.D.; MOERTEL, CHARLES G. M.D.

Anesthesiology:  
January 1987 - Volume 66 - Issue 1 - ppg 89-91

### Perioperative management Instructions/warning

Twenty years later, Drs Bhattacharyya, Davar, Dreyfus and Caplin admonished in the Journal, Circulation:

"Avoiding or minimizing the use of drugs known to precipitate mediator release such as opioids, the neuromuscular relaxant atracurium, and catecholamine producers like dopamine and epinephrine may reduce the risk of carcinoid crisis."<sup>48,49</sup>

Contemporary Reviews in Cardiovascular Medicine  
Carcinoid Heart Disease  
Sanjeev Bhattacharyya, MB, ChB, MRCP; Joseph Davar, MD, PhD; Gilles Dreyfus, MD, FRCS; Maryn E. Caplin, BSc (Hons), DM, FRCP

Circulation.  
2007; 116: 2860-2865  
doi: 10.1161/ CIRCULATIONAHA.107.701367

### Perioperative management Instructions/warning

And Drs Powell, Mukhtar and Mills commented upon the **alternative to adrenergic pressors for hypotension**:

"Reliable large bore access in case of rapid volume loss and the availability of fluid warmers and the use of a rapid infusion system are sensible standards."

Powell B, Al Mukhtar A, Mills GH  
Carcinoid: the disease and its implications for anaesthesia  
Contin Educ Anaesth Crit Care Pain (2011) 11 (1): 9-13.

### Postoperative management

- 9 - **Treatment of Carcinoid Crisis after surgery**— Same  
Treat hypotension with fluids and octreotide boluses/ Sometimes Solucortef is given in the post-op period.
- 10 - **When BP stable: Return patient to dry weight**  
**I write orders:**  
Daily Am weights – Often I'm the only one interested in this!  
Diurese to dry weight  
Monitor BP sitting and standing once/8-hour shift
- 11 - **Postoperative echocardiogram** — within 1 week of surgery  
4 chamber status  
immediate postoperative valvular status
- 12 - **Pre-dismissal instructions** to patient and family:  
Check weight and BP sitting and standing each AM  
Phone data to me daily.  
Physiotherapy is arranged at patient's home – **very important**

### Post-dismissal management

- 13 - **Follow-up every two weeks in office**  
Blood tests (weekly, at home or in our office)  
Nutritional assessment  
Decision re multitasking tumor-reductive procedure at 6-12 weeks post-op (avoid recurrence of carcinoid valvulopathy on prosthetic tissue valves)
- 14 - **Repeat echocardiogram and biomarkers at 4 weeks post-op**  
Recurrence of carcinoid valvulopathy as early as 3-4 months post-op (Drs Caplin, Davar et al)
- 15 — **Finally - Prepare** patient for multitasking tumor-reductive surgery or other tumor-directed procedure or therapy  
**If serotonin elevated, we urge entry into one of the two Telotristat trials**