

# Carcinoid Heart Disease and other Neuroendocrine Tumor Cardiac Complications

Jonathan Strosberg,  
Associate Professor  
Moffitt Cancer Center  
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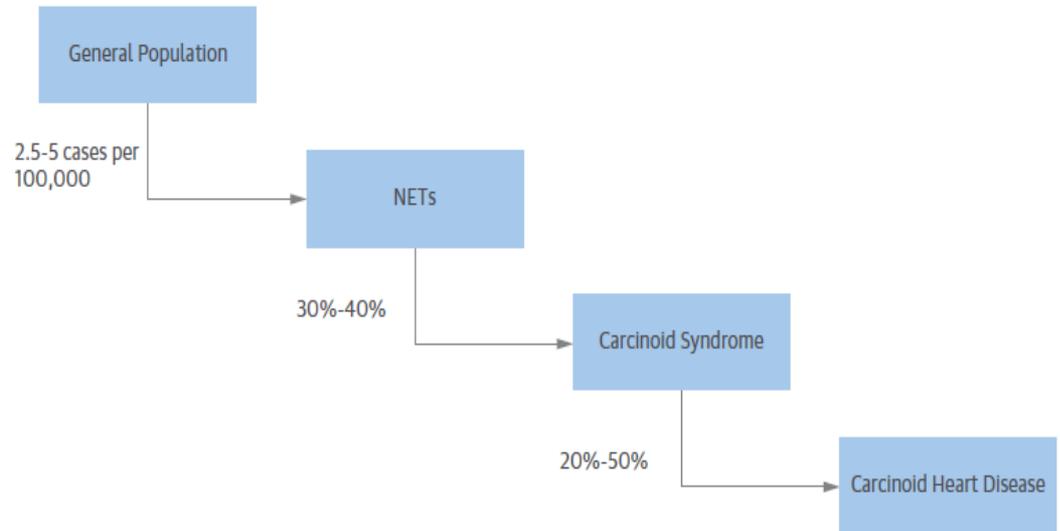
# Background

- Neuroendocrine tumors (NETs) are increasing in incidence.
- Metastatic NETs of the distal small intestine (midgut) produce serotonin and are typically associated with the carcinoid syndrome (flushing, diarrhea, wheezing).
- Carcinoid heart disease is a late manifestation of carcinoid syndrome.

# Incidence

- Older literature: Carcinoid heart disease occurs in 20-50% of patients with the carcinoid syndrome<sup>1</sup>
- Recent literature: Carcinoid heart disease develops in 10% of patients with metastatic midgut NETs<sup>2</sup>

**FIGURE 1** Schematic to Show Population Affected by NET, Carcinoid Syndrome, and Carcinoid Heart Disease



1. Moller et al. Circulation 2005; 112:332-37
2. Strosberg et al. J Clin Oncol. 2013 Feb 1;31(4):420-5
3. Davar et al J Am Coll Cardiol 2017 Mar 14;69(10):1288-1304

# Pathophysiology

- Degree of damage correlates with extent and duration of serotonin exposure (median 5HIAA >200mg/24h)
- Right sided valves (tricuspid, pulmonary) predominantly affected
- Left sided valves involved <10%, likely due to inactivation of serotonin in the pulmonary circulation

- Plaque-like deposits of fibrous tissue on the endocardium of valvular cusps, leaflets, papillary muscles, cords, and cardiac chambers
- Plaques composed of myofibroblasts, smooth muscle cells and extracellular components
- Serotonin is likely the causative factor; 5HT receptors abundant on heart valves
- Similar pathology seen with anorectic drugs fenfluramine and phentermine (fen-phen), also thought to be serotenergic



Carcinoid heart disease: Thickened and fibrotic pulmonary valve caused by fibroblast proliferation

1. Robiolio et al. Circulation. 1995 Aug 15;92(4):790-5
2. Batacharyya et al. Lancet 2009; 374:577

- Affected valves have white appearance
  - thickened leaflets
  - shortened chordae
  - thickened papillary muscles
- Plaque usually involves ventricular aspect of tricuspid valve and arterial aspect of pulmonic valve

# Signs/Symptoms

- Fatigue
- Dyspnea on exertion
- Edema
- Cardiac cachexia
- JVD (with prominent v wave)
- Murmur (accented by inspiration)

# Screening

- **NCCN<sup>1</sup>:** For patients with carcinoid syndrome, echo every 2-3 years or as clinically indicated
- **NANETS<sup>2</sup>:**
  - Annual echo in all patients with significant elevations of urine 5-HIAA (>5 x ULN)
  - Monitor patients with known early CHD more closely
  - No consensus on screening asymptomatic patients with mild elevations of urine 5-HIAA
- **Uptodate<sup>3</sup>:**
  - For patients with carcinoid syndrome, measure NT-proBNP levels.
  - Echo in anyone with signs/symptoms or NTproBNP >260ng/ml (or 31 pml/L)

1. Shah et al. J Natl Compr Canc Netw. 2018 Jun;16(6):693-702

2. Strosberg et al. Pancreas. 2017 Jul;46(6):707-714

3. Connolly Uptodate 2018

# NT-proBNP and echo findings

- NP-proBNP > 260 pg/ml
  - Sensitivity 69-82%
  - Specificity 80-91%
- Echo (*trans-thoracic*)
  - Thickening and retraction of tricuspid valve leaflets with associated tricuspid regurgitation  
*or*
  - Tricuspid valve stenosis
  - Immobility of pulmonary valve cusps (may be difficult to visualize)
  - Right ventricular volume overload and diastolic pressure elevation (late finding)

# Echo findings

## Tricuspid valve

- Thickening of the valve leaflets and subvalvular apparatus
- Diminished normal concave curvature of the leaflets
- Altered dynamic motion of the leaflets during diastole
- Fused and shortened chordae
- Retraction and reduced excursion of the valve leaflets
- Tricuspid regurgitation, ranging from mild to severe

## Pulmonary valve

- Diffusely thickened valve cusps
- Straightening of cusps
- Fixed, retracted, and thickened cusps
- Pulmonary regurgitation and/or (annular) stenosis

## Right atrium

- Dilated
- Inferior vena cava

## Right ventricle

- Dilated
- Reduced function

# Prevention

- Strategies to reduce circulating serotonin *likely* reduce development/progression of CHD.
  - Somatostatin analogs
  - Telotristat ethyl (oral serotonin inhibitor)
  - Hepatic transarterial embolization
  - Surgical debulking
  - Peptide receptor radiotherapy ( $^{177}\text{Lu}$ -dotatate)
- No evidence of reversal of CHD with medical treatments

Kulke et al. J Clin Oncol. 2017 Jan;35(1):14-23

O'Toole et al. Endocr Relat Cancer. 2003 Dec;10(4):463-8

Strosberg et al. N Engl J Med. 2017 Jan 12;376(2):125-135

# Cardiologic management

- Diuretics may improve symptoms, but may also result in decreased cardiac output

# Valve Replacement

- Consider in symptomatic patients with reasonably controlled metastatic disease
  - Symptomatic valve dysfunction
  - Decline in right ventricular function
- Typically replacement of tricuspid and pulmonary valves (unless clear uninvolved pulmonary valve)
- Need octreotide prophylaxis (iv 50-100mcg/h)

# Bioprosthetic vs. Mechanical Valve

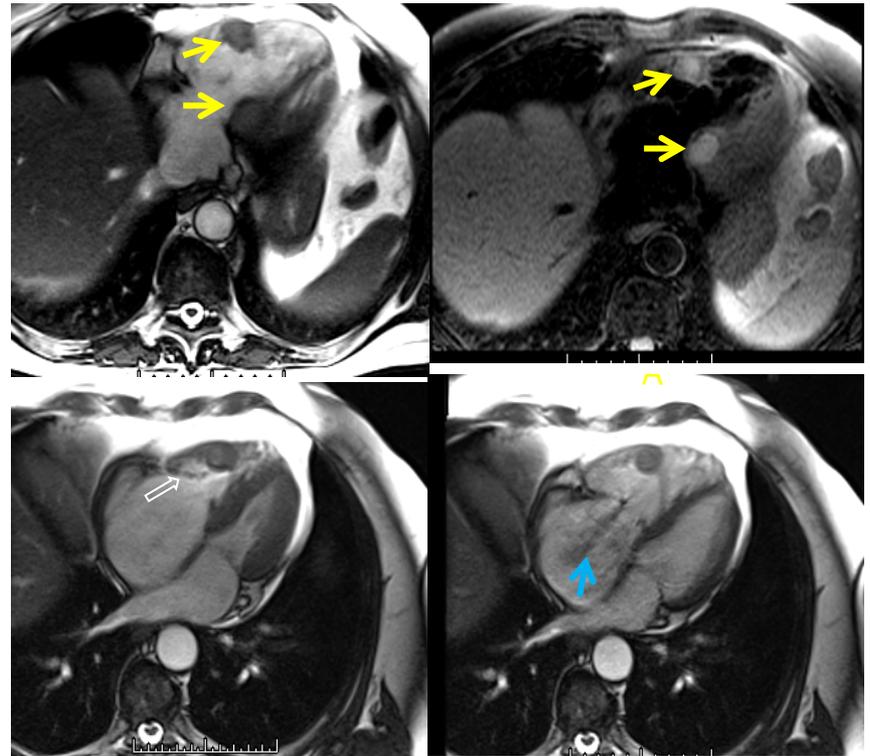
- Bioprosthetic: risk of degeneration caused by carcinoid heart disease
- Mechanical: increased risk of thrombosis (up to 4% a year). Also need for permanent anticoagulation (vs. 3-6 months with bioprosthetic)

# Prognosis

- Non-operative cases with severe carcinoid heart disease (NYHA class III or IV), median survival <1 year
- Operative mortality of about 5%
- With surgery, median OS improved from from 1.5 years in the 1980s, to 4.4 years in the late 1990s.

# NET Cardiac Metastases

- Rare occurrence (<5% of metastases)
- Reported as myocardial nodules or pedunculated masses
- Can be a/w pericardial effusions
- Resections and XRT have been reported



MRI images courtesy of Dr. Daniel Jeong