Valvular Heart Disease: Uncommon Etiologies
Radiation, Systemic Disease, and Drug-Induced

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DISCLOSURES

Relevant Financial Relationship(s)
None

Off Label Usage
None
Radiation-Induced Valvular Heart Disease

Radiation Induced Cardiac Disease

- Pancarditis: pericardial, myocardial, endocardial/valvular (fibroelastosis)
- Acute pericarditis during therapy
- Delayed pericarditis: constriction, pericardial effusion
- Cardiomyopathy: diastolic/systolic dysfunction
- CAD: intimal proliferation, endothelial dysfunction
- Conduction system defects
Radiation Induced Cardiac Disease
Risk Factors

- Total radiation dose
- Younger age during radiation therapy
- Higher percentage anteroposterior vs. tangential beam trajectory
- Anthracycline therapy: cardiomyopathy and valvular disease
- Smoking, hyperlipidemia, DM: CAD


Radiation Induced Cardiac Disease
Disease Associations

- Hodgkin’s lymphoma (most common)
- Breast cancer (left or right)
  Internal mammary chain therapy
- Esophageal cancer
- Non-Hodgkin’s lymphoma
- Lung cancer
- Thymic irradiation
Radiation Therapy for Hodgkin’s Lymphoma
Cardiovascular Effects in 404 Patients
(Treated 1962-1998)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Median Time After Therapy</th>
</tr>
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<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>10.4%</td>
<td>9 Yrs</td>
</tr>
<tr>
<td>Carotid ± Subclavian Disease</td>
<td>7.4%</td>
<td>17 Yrs</td>
</tr>
<tr>
<td>Significant Valvular Disease</td>
<td>6.2%</td>
<td>22 Yrs</td>
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Hull MC, et al. JAMA 2003; 290:2831

Radiation Therapy for Hodgkin’s Lymphoma
Clinically Significant Valvular Disease
25 Patients (6.2%); Involving 29 Valves
Predominant Lesion

- Aortic Stenosis (48%)
- Mitral Regurgitation (28%)
- Mitral Stenosis (10%)
- Tricuspid Regurgitation (10%)
- Aortic Regurgitation (4%)

Hull MC, et al. JAMA 2003; 290:2831
56 y/o Woman: Progressive DOE and angina
Radiation therapy for Hodgkin’s lymphoma at age 14

Mean MV gradient: 8 mmHg
56 y/o Woman: Progressive DOE and angina
Radiation therapy for Hodgkin’s lymphoma at age 14

Mean AV gradient: 57 mmHg
57 y/o Man: Recurrent Atrial fibrillation
Chest irradiation for non-Hodgkin’s lymphoma at age 45

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41 y/o Male: Exertional fatigue, presyncope, & TIA
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Carcinoid Syndrome
Carcinoid Syndrome

- Neuroendocrine neoplasm of small bowel (85%), stomach, rectum, bronchus (5%), ovary
- Enterochromaffin cell secretion:
  Serotonin (5-HT), bradykinin, histamine, prostaglandins and multiple other vasoactive agents

Carcinoid Syndrome Symptoms

- Flushing
- Urticaria
- Diarrhea
- Hypotension
- Bronchospasm

Syndrome present in 20-30% at diagnosis
Carcinoid Heart Disease

- Initial presentation of carcinoid disease in ~ 20% of patients; eventually occurs in over 50% with carcinoid syndrome

- Carcinoid plaque deposition (smooth muscle proliferation, myofibroblasts, elastic tissue); serotonin mediated (5-HT 2B receptor activation)

- Usually associated with hepatic metastasis; plasma serotonin and urinary 5-HIAA levels 2-4 x higher than in those without cardiac disease. Progression related directly to degree of elevation of urinary 5-HIAA.

Cardiac Involvement

- Tricuspid valve, leaflets, annulus, and support apparatus (> 95%)

- Pulmonary valve cusps and annulus (~50%)

- Left heart valves uninvolved unless:
  - R → L shunt (PFO)
  - Bronchial carcinoid
  - Marked ↑↑ in plasma serotonin/urinary 5-HIAA

- Endocardium of RA and RV, pulmonary arteries, vena cavae

- Myocardial metastasis (<5%)

59 y/o Man: Ileal carcinoid with hepatic & peritoneal metastasis; Urine 5-HIAA 381mg/24 hrs, (ref < 8 mg/24 hrs)
Severe (Torrential) Tricuspid Regurgitation
Systolic RV → RA pressure equalization

TR  CW Doppler

70 y/o Man: Ileal carcinoid with extensive hepatic metastases; severe dyspnea and right heart failure
70 y/o Man: Ileal carcinoid with extensive hepatic metastases; severe dyspnea and right heart failure

Pulmonary valve: CW Doppler
25 y/o Female: Primary ovarian carcinoid

Antiphospholipid Antibody Syndrome
Antiphospholipid Syndrome

• **Primary**

• **Secondary**
  (associated with systemic autoimmune disease; primarily systemic lupus erythematosus)

Antiphospholipid Syndrome

**Diagnosis: Clinical**

• Venous or arterial thrombosis (often recurrent, multiple locations):
  DVT (~30%), livedo reticularis (~25%),
  CVA (~15%), TIA (~10%), PE (~10%),
  superficial thrombophlebitis (~10%)

• Thrombocytopenia, hemolytic anemia

• Complicated pregnancies: multiple miscarriages, premature births due to placental insufficiency, pre-eclampsia, unexplained fetal death
Antiphospholipid Syndrome
Diagnosis: Laboratory

- Antiphospholipid antibodies to cardiolipin (aPL IgG and IgM), and other phospholipids
- Antibodies to Beta-2 Glycoprotein I
- Lupus anticoagulant activity (prothrombotic)

Endocardial disruption of valve coaptation margins

- Circulating antiphospholipid antibodies induce immune complex deposition, activate TNF and VCAM
- Valve endothelial activation, monocyte infiltration, intravalvular capillary thrombosis
- Fibrinous thrombotic vegetation deposition, lamination
- Leaflet thickening, fibrosis, retraction, regurgitation, (uncommonly stenosis)
Antiphospholipid Syndrome: Valvular Disease

- Prevalence: 60-80%
  MV > AV; rarely TV, PV
  Regurgitant >> stenotic

- High IgG aPL titer:
  increases risk of
  vegetations, severe
  valve regurgitation, and
  thromboembolism

28 y/o Woman: DOE and episodic visual deficits.
IgG aPL and IgG β2-GPI Ab >100, + Lupus AC
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28 y/o Woman: DOE and episodic visual deficits. IgG aPL and IgG β2-GPI Ab >100, + Lupus AC
51 y/o Housewife: Mild DOE, severe AR
51 y/o Housewife: Mild DOE, severe AR (IgG aPL Ab > 100 GPL)

Hypereosinophilic Syndrome (HES)
Hypereosinophilic Syndrome (HES) Diagnostic Criteria

• Persistent eosinophilia (> 1,500/µL) for ≥ 6 months

• Primary: myeloproliferative disorder

• Secondary: infectious, allergic, or systemic inflammatory


Stages of Cardiac Disease with HES

Necrotic Stage
Acute eosinophilic endocardial myocarditis

Thrombotic Stage
Thrombus formation over infiltrated endocardium

Fibrotic Stage
Endocardial thickening & endomyocardial fibrosis
Hypereosinophilic Syndrome (HES)
Cardiac Involvement: 40-60% of patients

LV > RV inflow apical thrombo-obliteration, endocardial thickening

2-D Echo & Doppler Findings
Restrictive diastolic dysfunction

Subvalvular thrombosis, leaflet entrapment
MV > TV Leaflets; MR&TR

42 y/o Man: Hypereosinophilic syndrome; heart failure and hypotension
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42 y/o Man: Hypereosinophilic syndrome; heart failure and hypotension
67 y/o Man: Anasarca and severe TR; HES due to Churg-Strauss syndrome

41 y/o Female: Refractory diarrhea and dyspnea; HES due to Strongyloides Stercoralis infection
41 y/o Female: Refractory diarrhea and dyspnea; HES due to Strongyloides Stercoralis infection

Drug-Induced Valvulopathy
Drug activation of valvular 5 – HT 2B receptors

G-regulatory protein dissociation activates protein and extracellular kinases, ↑↑ transforming growth factor β

Mitogenesis and proliferation of valvular interstitial cells (smooth muscle cells, myofibroblasts, and fibroblasts)

Diffuse expansion of collagenous extracellular matrix (glycosaminoglycans) with extensive fibrosis

Leaflet thickening/retraction; (overgrowth) valvulopathy

Drug-Induced Valvular Disease
Echocardiographic Findings

• Thickening and retraction of valve leaflets or cusps
  • No commissural fusion
  • Reduced mobility, restricted closure coaptation

• Thickened, fused, shortened MV/TV chordal support apparatus

• Variable regurgitation, rarely significant stenosis
55 y/o Female: NYHA Class III exertional dyspnea; history of Fen-Phen use x 18 months 5 yrs ago
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79 y/o Woman: Right heart failure; longstanding Cafergot use for refractory migraine headaches
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Drugs with Potential to Induce Valvulopathy
Strong 5-HT2B Agonist Drugs Still Available

- Guanfacine (Intuniv, Tenex)  ADHD
- Fenoldopam (Corlopam)  Severe HTN
- Quinidine  Arrhythmia
- Ropinirole (Requip)  Parkinson’s, Restless legs
- Oxymetazoline (Afrin, Visine, Vicks products)
- Xylometazoline (in hundreds of decongestants)

Elangbam CS. Toxicologic Pathology 2010; 38: 837

Rave Party
**MDMA (3,4-Methylenedioxymethamphetamine)**

Echo Findings with “Ecstasy” Abuse

<table>
<thead>
<tr>
<th></th>
<th>MDMA Users (n=33)</th>
<th>Controls (n=29)</th>
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<tbody>
<tr>
<td>Duration of use</td>
<td>6.1 ± 3.4 yrs</td>
<td>0 yrs</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>24.3 ± 3.1 yrs</td>
<td>25.6 ± 3.1 yrs</td>
</tr>
<tr>
<td>MR ≥ Grade 2/4</td>
<td>4 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Restricted MV motion</td>
<td>7 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>TR ≥ Grade 2/4</td>
<td>13 (45%)</td>
<td>0</td>
</tr>
<tr>
<td>Restricted TV motion</td>
<td>7 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>AR ≥ Grade 1/4</td>
<td>4 (14%)</td>
<td>0</td>
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• Prevalence of MDMA abuse: 0.4 – 6% worldwide

Droogmans S, et al. Am J Cardiol 2007; 100: 1442

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**Valvular Heart Disease: Uncommon Etiologies**

• Multi-valvular heart disease can be associated with radiation therapy, certain systemic diseases, and 5-HT 2B agonist drugs

• Characteristic echocardiographic findings can prompt the correct, and even an entirely unsuspected diagnosis
Valvular Heart Disease: Uncommon Etiologies
Radiation, Systemic Disease, and Drug-Induced

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(One Disclosure)

Radiation Therapy for Hodgkin’s Lymphoma
Prevalence of Valvular Disease

Heidenreich PA, et al. JACC 2003; 42: 743
Radiation Therapy for Hodgkin’s Lymphoma
Valvular Calcification (294 ASxtic Patients; 42 ± 9 Yrs of age)

Years Since Radiation

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<th>Calcification of AV, MV, ± intervalvular fibrosa</th>
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<tr>
<td>≤ 5 Yrs</td>
<td>39%</td>
</tr>
<tr>
<td>&gt;20 Yrs</td>
<td>90%</td>
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• Unusually marked calcification of AV-MV intervalvular continuity extending onto anterior mitral leaflet in 26%; an isolated finding in 8%

Heidenreich PA, et al. JACC 2003; 42: 743

68 y/o Woman: Ovarian carcinoid, mesenteric & mediastinal metastases; no hepatic lesions
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Mean MV gradient = 6 mmHg
56 y/o Woman: Progressive DOE and angina
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Carcinoid Heart Disease
Tricuspid Valve

- Thickened, retracted, and immobile leaflets: incomplete coaptation
- Severe TR; functional tricuspid inflow stenosis
- RV & RA enlargement 2° to volume overload; variable RV dysfunction
Carcinoid Heart Disease
Pulmonary Valve

- Thickened, retracted, and immobile cusps: incomplete coaptation
- Pulmonary annular constriction ‘hourglass’
- Severe PR, pulmonary outflow stenosis

54 y/o Woman: Heart murmur evaluation; ergonovine therapy for migraines x 20 yrs
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28 y/o Woman: DOE and episodic visual deficits. IgG aPL and IgG β2-GPI Ab >100, + Lupus AC
40 y/o Female: Chest pain, grade II/IV AR, mean gradient = 35 mmHg

Mean AV gradient: 57 mmHg
Antiphospholipid Syndrome: Therapy

Long-term moderate dose warfarin (INR 2-3) after initial thrombosis event. Antiplatelet therapy added with arterial events. High dose A/C if recurrence.

Valvular Lesions: Variable or no response to even high dose anticoagulation ± antiplatelet therapy

Steroids, IVIG, immunomodulation

Lim W, et al. JAMA 2006; 295: 1050
Cervera R. Thrombosis Res. 2004; 114: 501
Antiphospholipid Syndrome: Valvular Disease

- Valve thickening and distortion by layers of organized thrombus
- Appears rheumatic; but minimal calcium, no subvalvular lesions
- Prevalence: 60-80%
  MV > AV; rarely TV, PV
  Regurgitant >> stenotic

Cervera R. Thrombosis Res. 2004; 114: 501

Mean mitral gradient 6 mmHg (70 bpm)
40 y/o Female: Chest pain, grade II/IV AR, mean gradient = 35 mmHg