Chronic Thromboembolic Disease

Diagnosis
Prevention
Treatment
Surgical
Nonsurgical

Chronic Thromboembolic Disease Definition

- Pulmonary Hypertension due to chronic thromboembolism 6 months post acute PE:
  - Hemodynamic
    - Pulmonary Hypertension (RHC)
      - PAM >25 mmHg
      - PCW < 15 mmHg
      - PVR > 2-3 Woods
    - Anatomic (Pulmonary Angiography)
      - Persistent pulmonary vascular defects

45 yo female with PH (PAM 40, PCW 12).
What test is the best screen for CTE?

a. D-dimer
b. Ventilation Perfusion Scan
c. CT Chest Angiogram
d. Pulmonary Angiogram
V/Q scan has High Discriminative Value in Patients with Pulmonary Hypertension

<table>
<thead>
<tr>
<th>V/Q scan category</th>
<th>Very low/normal (N=36)</th>
<th>Low (N=10)</th>
<th>Intermediate (N=1)</th>
<th>High (N=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PHT (n=25)</td>
<td>0</td>
<td>33</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic thromboembolic PHT (n=25)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Nonthromboembolic secondary PHT (n=13)</td>
<td>0</td>
<td>10</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

PHT = pulmonary hypertension; V/Q = ventilation-perfusion


V/Q Scan is More Sensitive than Chest CT scan for Detection of CTE

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/Q (10)</td>
<td>97.4</td>
<td>95.2</td>
<td>91.3</td>
<td>89.3</td>
<td>91.1</td>
</tr>
<tr>
<td>V/Q (2)</td>
<td>97.1</td>
<td>95.2</td>
<td>91.3</td>
<td>89.3</td>
<td>91.1</td>
</tr>
<tr>
<td>CTPA</td>
<td>90.5</td>
<td>94.6</td>
<td>93.0</td>
<td>99.3</td>
<td>90.5</td>
</tr>
</tbody>
</table>

*Interimmediate with high probability scans as indicative of CTEPH.
Only high-probability scans as indicative of CTEPH.
NPV = negative predictive value; PPV = positive predictive value.


Chest CT Aids in Differential Diagnosis

N= 227 Patients
76 CTEPH
149 non CTEPH

Van Es et al Chest 2013
Fifth World Symposium on Pulmonary Hypertension

- Suspect
  - Echocardiogram
  - V/Q scan
- Confirm
  - Right Heart Catheterization
  - Pulmonary angiogram (or CTA, MRA)
- Assess Risk
  - Hemodynamics
  - Comorbidities
  - Surgeon/CTEPH team Experience

Kim et al JACC 2013

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What test is the best screen for CTE?

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c. CT Chest Angiogram
d. Pulmonary Angiogram

Risk Factors for CTEPH

- Venous thromboembolism
- Prior pulmonary embolism
- No prior pulmonary embolism
- New onset PH after acute pulmonary embolism
- Chronic medical conditions
  - Pulmonary hypertension associated with chronic obstructive pulmonary disease
  - Chronic obstructive pulmonary disease
- Events
  - Thrombotic events
  - Ischemic events
  - Hemorrhagic events
  - Systemic events
- Genetic factors
  - Factor V Leiden
  - Prothrombin G20210A
  - Abnormal coagulation proteins

Piazza et al NEJM 2011
Risk Factors for CTEPH

- 3.8% of Pulmonary Embolism develop CTE
  - Recurrent PE
  - Large PE and Hemodynamic Significant (PAS >50mmHg)
- Chronic Inflammatory Conditions
- Lysis resistant Fibrinogen

67 yo Female with Submassive PE

- 2-3 d of SOB
- 1 month ago received Hip Replacement
- History of HTN, OSA, Obesity, A Fib with prior AC complicated by vegetarian diet
- BP 108/69 P 115 SaO2 94% on 4 Liters
- Troponin 0.34, Cr 1.7
- LE doppler: popliteal DVT
What would be your next therapeutic maneuver?
1. Continue same dose with heparnoid and warfarin overlap for 5 days until therapeutic then warfarin for 3 months
2. Thrombolytic half dose (50 mg) over 2 hours
3. Thrombolytic at full dose (100 mg) over 2 hours
4. Heparinoid for 5 days followed by Factor X inhibitor maintenance for 3 months
5. Heparinoid for 3 months

Pulmonary Embolism
Resolution
• Resolution
  – 36% Day 5; 52% day 14, 73% Mo 3, 76% Yr 1
• Pulmonary Hypertension
  – 27% of 144 patients treated with heparin have higher than baseline Echocardiographic PAS at 6 months (only 7% PAS>40) of which 46% were symptomatic
• Chronic Pulmonary Thromboembolism 4%

Kline et al Chest 2009
Pulmonary Hypertension 6 Months Post Sub-Massive Pulmonary Embolism

Kline et al Chest 2009

Moderate Pulmonary Embolism Treated with Thrombolysis “MOPPET”

- Moderate PE:
  - Symptomatic
  - Normotensive
  - 70% involvement of > 2 lobar or main pulmonary artery

Sharifi et al Am J Cardiol 2013

MOPPET Protocol

TPA 50 mg (10 mg over 1 minute then 40 mg over 2 Hr)
Heparin 80 U/kg bolus Infusion 18 UI/hr
Lovenox 1 mg/kg max 80 mg
Heparin 70 U/kg not to exceed 8000U
Infusion 100U/hr not to exceed 1000U/hr
For 3 hours

Sharifi et al Am J Cardiol 2013
**Moderate PE and Reduced Dose TPA**

Primary end points at 28 ± 5 mo of follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>TG (n = 58; 100%)</th>
<th>CG (n = 56; 100%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>9 (16%)</td>
<td>32 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary hypertension plus recurrent</td>
<td>9 (16%)</td>
<td>35 (63%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pulmonary artery systolic pressure ≥40 mm Hg.

**Moderate PE and Reduced Dose TPA**

Secondary end points

<table>
<thead>
<tr>
<th>Variable</th>
<th>TG (n = 62; 100%)</th>
<th>CG (n = 61; 100%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pulmonary embolism</td>
<td>0 (5%)</td>
<td>3 (5%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1 (1.6%)</td>
<td>3 (5%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total mortality plus recurrent</td>
<td>1 (1.6%)</td>
<td>6 (10%)</td>
<td>0.049</td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>2.2 ± 0.5</td>
<td>4.9 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n (%).

**Edoxaban v Warfarin in PE**

![Graph comparing Edoxaban and Warfarin in PE over time.](image)
Edoxaban Reduced Recurrence in Patients with Sub-massive PE

BNP > 500 or CT RV enlargement

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban (n=454)</th>
<th>Warfarin (n=484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>15 (3.3%)</td>
<td>30 (6.2%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.4%</td>
<td>1.6%</td>
</tr>
</tbody>
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5. Heparinoid for 3 months

Hospital Course

- IV Heparin started
- Patient received TPA 50 mg IV with improvement in symptoms, P reduced to 84, and without bleeding
- Following 5 days Heparin she received Rivaroxaban 15 mg Bid for 21 days then 20 mg q d
CTEPH Treatment

Prevention

?Proposed Treatment Strategy

• Half dose Thrombolytics vs Heparinoid alone
• Factor X inhibitor v Warfarin s/p heparinoid for 5 days

CTEPH Treatment

• Surgical
• Medical
  – Anticoagulation
  – Vasodilators

65 yo Female with PH

• WHO 3
• PMHx DVT in 70’s, PE 9/09 Rxed Heparin + Warfarin
• RHC 10/10 PA 67/34 PAM 48 PCW 7
• PVR 6 Woods
Diagnosed with CTEPH
What would be your next RX?
1. Begin Sildenafil
2. Refer to CV Surgery
3. Begin Bosentan
4. Pulmonary Rehab
5. All of above

CTEPH Treatment
• Surgical Thromboendarterectomy
  – Treatment of Choice
  – Survival at 3 years 89% operated vs 70% for non-operative group
• Medical Survival
  – Non-operative Candidate 37%
  – Persistent PH 17%

Simonneau et al Am J Resp Crit Care 2013
Pepe-Zaba et al Circulation 2011

Pulmonary Hypertension
Pathophysiology

Plazza et al NEJM 2011
Organized Thrombus in Pulmonary Artery of Patient CTEPH

Piazza et al NEJM 2011

Surgical Specimen Post Pulmonary Thromboendarterectomy

Piazza et al NEJM 2011

Surgical Specimens following Pulmonary Thromboendarterectomy

CT Scan Before and After Thromboendarerectomy

Hemodynamic Response to Thromboendarectomy

Hemodynamics Post Pulmonary Thromboendarerectomy

Mortality Following Surgical Endarterectomy

Patient was seen at Mayo Clinic

- They deemed her a non-operative candidate and recommended:
  - Bosentan
  - Anticoagulation
  - Pulmonary rehab

You would do the following?

1. Continue warfarin
2. Add Bosentan following determination of LFTs and pregnancy status
3. Seek a second opinion
The 5th World Symposium on Pulmonary Hypertension

Pulmonary Hypertension Pathophysiology

Plexiform Lesions in CTEPH
Medical treatment
Persistent PH and/or Inoperable Dx

- Anticoagulant
- Vasodilator
  - Bosentan
    - Improved Hemodynamics
  - Riociguat
    - Improved hemodynamics
    - Improved 6 " walk

Riociguat
Mechanism of Action

Riociguat Improves 6 Minute Walk in CTEPH

Ghofrani et al NEJM 2013
CTEPH Treatment

• Proximal Disease
  • Warfarin
  • IVC Filter
  • Pulmonary Thromboendarterectomy
• Distal Inoperable Disease/Persistent PH
  • Warfarin
  • Vasodilators

Dana Point Conference

35 yo Marathon Runner

• 1 week of calf pain
• Last Night SOB, chest pain
• P115, SBP 150, RR 24
• PT 13.4 Hgb 13.9, Plts 185, WBC 8
• Heparin was administered
CTEPH Treatment

- Surgical: Treatment of choice
- Nonsurgical:
  - Non-operative Candidate:
    - Second Opinion
  - Persistent PH post Surgery