”I’m Short of Breath”
Systematic Evaluation, Workup and Lessons
Borrowed from Advanced Dyspnea Clinics

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Conflict of Interest Statement

– No conflicts relevant to this talk
Objectives

• At the end of this lecture, participants should be able to:
  – Review standard evaluation of the dyspneic patient
  – Identify common causes of chronic dyspnea
  – List current causes of "difficult to diagnose" chronic dyspnea
  – Discuss advanced imaging, exercise and cardiopulmonary testing available for difficult to diagnose chronic dyspnea.
Introduction, Definitions, Background
Variable Definitions Of Dyspnea

• Unpleasant or uncomfortable respiratory sensations
• Difficult, labored, uncomfortable breathing
• Awareness of respiratory distress
• The sensation of feeling breathless or air hunger
• An uncomfortable sensation of breathing

• ATS guidelines: subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity

ATS. AJRCCM, 1999.
Dyspnea Symptom Prevalence

• Epidemiology of the problem:
  – 9-13% community residing adults have mild-moderate dyspnea
  – Age 40 or over: 15 – 18%
  – Age 70 or over: 25 – 37%

• Responsible for 3 – 4 million yearly ED visits

Parshall, AJRCCM 2012:185;435
Mechanisms Of Dyspnea: Respiratory Center Output

• Chemoreceptors
  – Peripheral: carotid bodies, aortic arch
    • Sense changes in PO2, acidosis, hypercapnea
  – Central: medulla
    • pH and PCO2 changes

• Hypercapnea
  – Potent stimulus of dyspnea

• Hypoxia
  – Less potent stimulus than hypercapnea

Mechanisms Of Dyspnea: Stimulation Of Mechanoreceptors

• Mechanoreceptors
  – Upper airway
  – Pulmonary receptors
    • Limitations of movement exacerbate dyspnea
    • The sensation of dyspnea varies with activation
  – Chest wall receptors
    • Restricted motion exacerbates dyspnea
    • Redundant to pulmonary receptors

Pain and Dyspnea in the **Anterior Insula.** One of the key brain regions activated in both dyspnea and pain is the anterior insula. The “P” symbols show the locations of pain activations of the insula in a transverse slice at Z=+8. Pain data from various studies summarized by a meta analysis ([Peyron et al. 2000](https://example.com)). The larger circle labeled “D” shows the area activated by dyspnea ([Banzett et al. 2000](https://example.com)).

Lansing, Respir Physiol Neurobiol. 2009:167(1);53-60
Case

• 60 y/o with 2-3 years of increasing dyspnea manifest as insidious onset chest tightness/breathlessness chronic and present consistently at ascending 1 flight of stairs or equivalent.

• (-) Chest pain
• (-) cough or wheeze
• Intermittent trace edema (resolves)
• All other ROS (-)
Case

• Controlled essential hypertension, Treated and compliant OSA, dyslipidemia, Type II DM with no complications, hypothyroidism on replacement
• Social history non-smoker, no exposures, no hobby exposures, retired floor nurse
• Family history CV disease
• Exam: BMI = 33, SpO2 = 98%
• Labs: Normal
What next?

A) Spirometry
B) Echo
C) CXR
D) Stress Testing
E) CT Chest
F) 6 Minute Walk Testing
G) None of the above
H) All A-F
Traditional Approach to the Patient with Chronic Dyspnea
Typical Stepwise Evaluation in Chronic Dyspnea

- **Initial Evaluation**
  - History
  - Exam
  - Initial Testing

- **Review**
  If secure diagnosis treat/refer for treatment
Typical Stepwise Evaluation in Dyspnea

- **Initial Evaluation**
  - History
  - Exam
  - Initial Testing

  **Review**

  If secure diagnosis treat/refer for treatment

  **Refer**

  - Cardiology
  - Pulmonary
Typical Argument Among Consultants: Is It The Heart or the Lungs?
Typical Outcome of the Process in Some (Many) Cases

Refer → Evaluation → Review
Typical Outcome of the Process in Some (Many) Cases
Clues, Pearls and Protocols to Help Unravel Chronic Dyspnea
My Approach to Chronic Dyspnea

• Know what you are up against
• Play the Odds
• Protocolize the Workup
• Be aware of advanced specialty diagnostics (Dyspnea Center Techniques)
Know What You are up Against: Differential Diagnosis of Chronic Dyspnea

• Cardiac
  – Heart failure
  – Coronary artery disease
  – Arrhythmia
  – Pericardial disease
  – Valvular heart disease

• Pulmonary
  – Chronic obstructive pulmonary disease
  – Asthma
  – Interstitial lung disease
  – Pleural effusion
  – Pulmonary hypertension
  – Malignancy
  – Bronchiectasis

• Non-cardiac/Non-pulmonary
  – Thromboembolic disease
  – Psychogenic
  – Deconditioning
  – Obesity
  – Anemia
  – GERD
  – Metabolic conditions
  – Cirrhosis
  – Thyroid disease
  – Neuromuscular
  – Chest wall
  – Upper airway
  – Medications
Play the Odds:

1) Where are you?
2) What do you see?
3) When did it/does it happen?
## Playing the odds: 1) Where are you?

<table>
<thead>
<tr>
<th>Rescue service</th>
<th>Emergency room</th>
<th>General practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure (15–16%)</td>
<td>COPD (16.5%)</td>
<td>Acute bronchitis (24.7%)</td>
</tr>
<tr>
<td>Pneumonia (10–18%)</td>
<td>Heart failure (16.1%)</td>
<td>Acute upper respiratory infection (9.7%)</td>
</tr>
<tr>
<td>COPD (13%)</td>
<td>Pneumonia (8.8%)</td>
<td>Other airway infection (6.5%)</td>
</tr>
<tr>
<td>Bronchial asthma (5–6%)</td>
<td>Myocard. infarction (5.3%)</td>
<td>Bronchial asthma (5.4%)</td>
</tr>
<tr>
<td>Acute coronary syndrome (3–4%)</td>
<td>Atrial fibrillation or flutter (4.9%)</td>
<td>COPD (5.4%)</td>
</tr>
<tr>
<td>Pulmonary embolism (2%)</td>
<td>Malignant tumor (3.3%)</td>
<td>Heart failure (5.4%)</td>
</tr>
<tr>
<td>Lung cancer (1–2%)</td>
<td>Pulmonary embolism (3.3%)</td>
<td>Hypertension (4.3%)</td>
</tr>
</tbody>
</table>

Playing the Odds:
2) What do you see?

Playing the Odds: 3) When did it/does it happen?

- **Temporal**
  - acute onset, vs. chronic (present for more than four weeks), vs. acute worsening of pre-existing symptoms
  - intermittent vs. permanent
  - episodic (attacks)

- **Situational**
  - at rest
  - on exertion
  - accompanying emotional stress
  - depending on body position
  - depending on special exposure(s)

Berlinger D. et al. Dtsch Arztebl Int. 2016 Dec; 113(49): 834–845
Protocolize the Workup
“Don’t miss the easy stuff”
Example of Protocolized Chronic Dyspnea Workup

**TIER I**
- H&P with dyspnea index.
- Labs: Chem Complete, CBC, TSH, BNP
- PFTs: Spirometry, Lung Volumes, DLCO, BPC
- CXR

**TIER II**
- Cardiopulmonary Exercise Testing (CPET)

**TIER III**
- Pulmonary: CT Chest, V/Q, Bronchoscopy, Thoracentesis
- Cardiac: Stress Echo, Nuclear Stress Test, Cardiac Catheterization
- Others: GI

Typical Dyspnea Evaluation and Differential Diagnosis
Alternate “Level” Testing Algorithm

- **Step 1**
  - CBC with differential cell count, a chemistry panel that includes
  - renal and liver function tests, thyroid function tests
  - Chest radiograph
  - Electrocardiogram
  - Spirometry with pulse oximetry

- **Step 2**
  - Complete pulmonary function tests (spirometry before and after
    - Administration of a bronchodilator, measurement of lung volumes,
    - Diffusing capacity, and flow volume curves)
  - Chest CT scan (high resolution and/or CT arteriography)
  - B-type natriuretic peptide measurement and transthoracic
    - Echocardiography

- **Step 3 - CPET**

Problems with These Approaches

• No accounting for difficulties in some diagnoses
  – HFPEF
  – Pulmonary Arterial Hypertension
  – Coronary Disease
  – Vocal Cord Dysfunction

• No accounting for diversions of diagnoses due to comorbidities

• Tests are performed at rest!

• Some patients will still remain undiagnosed
Specialty Referral to a Dyspnea Center: Approach to the Patient with Chronic Undefined Dyspnea After Initial Testing
Alternate Approach to Cardiopulmonary Dysfunction

- Cardiac Dysfunction
- Pulmonary Parenchymal Disease
- Circulatory
- Deconditioning
- Metabolic/Hematologic
- Psychiatric
The Dyspnea Spiral

Differential Diagnosis of Chronic Dyspnea

- **Cardiac**
  - Heart failure
  - Coronary artery disease
  - Arrhythmia
  - Pericardial disease
  - Valvular heart disease

- **Pulmonary**
  - Chronic obstructive pulmonary disease
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  - Bronchiectasis

- **Non-cardiac/Non-pulmonary**
  - Thromboembolic disease
  - Psychogenic
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  - Obesity
  - Anemia
  - GERD
  - Metabolic conditions
  - Cirrhosis
  - Thyroid disease
  - Neuromuscular
  - Chest wall
  - Upper airway
  - Medications
Causes of Dyspnea in a Pulmonary Clinic

- **Non-Cardiorespiratory Causes**
  - 64%

- **Cardiovascular and Circulatory Diagnoses**
  - 33%

- **Respiratory Diagnoses**
  - 3%

Pratter et al. Respiratory Medicine Volume 105, Issue 7, Pages 1014–1021
Our Approach To The Patient with Chronic Cryptogenic Dyspnea – Initial Testing and Review

- History and physical
- ECG
- Spirometry, Lung volumes, pulse oximetry rest and ambulatory
- CXR/CT scan
- Echocardiogram with bubble contrast if hypoxia or desaturation, +/- exercise
- Cardiopulmonary exercise testing with spirometry
Why evaluate with exercise?

- “Dyspnea is a complex symptom that potentially warns of a critical threat to homeostasis and thus frequently leads to adaptive responses (such as rest)”.

- Exercise is the ideal stimulus to interrogate the cardiovascular system
  - Increases oxygen consumption and minute ventilation by 3 – 15x baseline utilization
  - Improves signal to noise ratio of test

- Most patients are not dyspneic at rest. Why not test them when they have symptoms?

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1 Parshall, AJRCCM 2012:185;435
Consider Advanced Non-Invasive/Minimally Invasive Studies in Dyspnea Evaluation

- Complete PFTs (Dco, Lung volumes, Flow-volume loops, Resp. pressures, ABG)
  - During exercise
  - Methacholine testing
  - Positional
- Airway inspection +/- Exercise
  - Endoscopic
  - Dynamic CT
- Echocardiogram
  - Exercise
  - Bubble studies
Consider Invasive Procedures in Dyspnea Evaluation

- Cardiac Catheterization
  - RHC
    - Volume Loading
    - Nitroprusside
    - NO Challenge
    - Simple Exercise
  - LHC
  - iCPET

- Muscle Biopsy

- Open Lung Biopsy
Non-Invasive Cardiopulmonary Exercise Testing
Cardiopulmonary Exercise Test (CPET)
# Common Variables Measured During CPX

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ Peak (O₂ ml/kg/min)</td>
<td>Highest demonstrable VO₂</td>
<td>Expression of aerobic exercise capacity</td>
</tr>
<tr>
<td>VT (O₂ ml/kg/min)</td>
<td>VO₂ at which there is an accelerated rise in VE &amp; VCO₂ relative to VO₂</td>
<td>Measure of fitness (usually about 50-65% of VO₂ Max)</td>
</tr>
<tr>
<td>RER (VCO₂ / VO₂)</td>
<td>Ratio at max exercise</td>
<td>Indicator of subject effort (RER &gt;1.10)</td>
</tr>
<tr>
<td>VE / VCO₂</td>
<td>Efficiency of pulmonary clearance of CO₂ during exercise</td>
<td>Reflects V/Q matching (can be used for severity index)</td>
</tr>
<tr>
<td>Breathing reserve</td>
<td>Relation of max VE and pre-test max voluntary ventilation (MVV)</td>
<td>Index of physiologic reserve of lung (low in COPD and trained athletes)</td>
</tr>
<tr>
<td>Oxygen Pulse (VO₂/HR)</td>
<td>Ratio of oxygen consumption to HR</td>
<td>Surrogate Marker for Stroke Volume</td>
</tr>
</tbody>
</table>

Modified from: Siestema Circ. 2011;123:668-680
Diagnostic Patterns of Abnormal CPET Results
Exercise Echo Testing
What Does DHF Look Like On Echo?

Nagueh. JASE, 2009.
Diastolic Stress Echo

E/e’ 17

E/e’ 24

Peteiro, JASE 2008;21:178
Pulmonary Hypertension Stress Echo

Rest 4 Chamber View

Peak Exercise 4 Chamber View
Additional Exercise Echo Studies

• Assess wall motion abnormalities
• Assess valvular gradients and function with exercise
• Check bubble study to assess PFO shunting during exercise with hypoxic patients with minimal shunt during rest
Invasive Cardiopulmonary Exercise Testing
UH iCPET
I-CPET Allows for Hemodynamic Phenotyping

- Peak Exercise mean PAP and LAP (via PCWP)
- Peak Exercise mixed venous O2 saturation
- $\Delta \text{CaO}_2 - \text{CvO}_2$ gradient
- Fick Cardiac Output
- Pulmonary Vascular Resistance: PVR = (mPAP – LAP)/CO
- $\Delta \text{mPAP (mm Hg)} / \Delta \text{Cardiac Output (L/min)}$
The MGH CPET lab performed 406 studies over 3 year period.

Each patient had RHC, A-line placed and CO calculated by first pass radionuclide ventriculography.

75% of studies performed to evaluate dyspnea of uncertain etiology.
PA pressure normal response to exercise
A diagnostic algorithm for interpreting iCPET results.

Exercise Hemodynamics of HFpEF

Borlang, BA et al. Circ Heart Fail. 2010 Sep;3(5):588-95
UH Dyspnea Program, Summary and Conclusions
Case Revisited

- Patient underwent Left Heart cath through wrist. Normal coronaries with LVEDP of 14.
- iCPET with Arterial Line and Swan Ganz catheter in place with gas exchange.
  - MVO2 = 16 ml/kg/min (60% predicted)
  - Normal BP and HR response
  - Normal Vt, RR and Respiratory Reserve, normal spirometry at peak exercise
  - Anaerobic Threshold Consistent with Deconditioning
Case Revisited

• $\text{Ve/CO}_2 = 35$
• Normal CI, PAP 35/13, RAP = 6 mm Hg
• PCWP 13->28 mm Hg with exercise

• Diagnosis = Heart Failure with Preserved Ejection Fraction (HfPEF)
Causes of Dyspnea in UH Program

• Cardiac
  – Heart Failure (HFPEF)
  – Chronotropic incompetence
  – Undiagnosed critical coronary artery disease
  – Deconditioning

• Pulmonary and Airway
  – Asthma
  – IPF
  – Vocal Cord Dysfunction
  – Diaphragm Paralysis

• Others
  – Metabolic Acidemia
  – Probable mitochondrial abnormality

• Many Patients with multiple issues
Conclusions

• Dyspnea is a symptom with multi-organ system origins
• A step-wise approach to the dyspneic patient improves diagnostic accuracy
• Exercise is an important stressor to diagnose some cardiac and pulmonary causes of chronic dyspnea.
• In patients with both heart and lung disease, invasive cardiopulmonary exercise allows for determining which may be predominant.
Summary of Summary

• Know what you are up against
• Play the Odds
• Protocolize the Workup (Don’t miss the easy stuff)
• Be aware of advanced specialty diagnostics (Dyspnea Center Techniques)
History & Physical

• 75 y/o with years of dyspnea, worsening in last 2-3. Ex smoker 3 PPD, quit 20 years ago. Recently admitted with heart failure. History of OSA non-compliant with meds. No oxygen use. Occasional wheeze per patient. Difficulty breathing when lying flat on back. Chronic bronchitis

• BMI = 46, JVD 9 cm, absent BS right base, few scattered very soft wheezes, partially cleared with cough

• 2-3+ edema to knees
Summary of Workup (Old and New)

- Walks 69 m in 6 minutes, SpO\textsubscript{2} 97-> 87%, BORG 2-5, HR 84->96
- Afib with ICD/Pacer, HfREF 30%, Mild MR
- OSA with AHI 35, (58 in REM)
- Combined restrictive and obstructive PFTs with TLC 55%
- Chest CT with evidence amiodarone changes
- V/Q (-) for matched perfusion defects
- Normal TSH, HCO\textsubscript{3}, CBC, PO\textsubscript{2} = 68 mm Hg
- Abnormal CXR
Abnormal CXR
Abnormal Diaphragm
Flourography: “Sniff Test”
Subdivisions of Dyspnea

EF = 30%
Chronotropic incompetence
Poorly controlled BP
OSA worsening above
Mitral regurgitation

Obesity and deconditioning

Paralyzed HD
Component COPD ad
Bronchospasm
Amiodarone lung
Undiagnosed desaturation with ambulation

Cardiac
Pulmonary
Deconditioning
Case 3: History and Physical

- 52 y/o with approximately 1 year of insidiously increasing SOB. She feels that her heart "races" when she performs heavier exercise. Denies edema, wheezing, chest pain, weakness.
- No previous cardiopulmonary disease
- PMHx only for Raynaud’s without other rheumatologic manifestations with the exception of pleurisy approximately 9 months ago evaluated by CTPA which was (-)
- Remote 2 pk/year ex-smoker
- Used to powerwalk 2 years ago, now walks more slowly, no more than 1 mile.
- Exam unremarkable except for trace pedal edema
Workup

• Spirometry – normal
• 6 Minute Walk Testing (532m [416 predicted], SpO2 99->96%, HR 60->122, BORG = 0->3, Heart Rate recovery not done.
• Stress testing – RVSP = 42 mm Hg, no wall motion abnormalities, normal LV, LA without evidence diastolic dysfunction
• R and L Heart Cath with simple exercise
  – No CAD
  – PCWP 12
  – Mean PAP = 20 mm Hg
  – Exercise with arm curls Mean PAP = 31 mm Hg, PAOP not done.
### CPET

<table>
<thead>
<tr>
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<th>Rest</th>
<th>AT</th>
<th>Peak VO₂</th>
<th>%Pred</th>
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<tbody>
<tr>
<td><strong>Time</strong></td>
<td>0</td>
<td>3.08</td>
<td>5:57</td>
<td></td>
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<tr>
<td><strong>Work (Watts)</strong></td>
<td>0</td>
<td>42</td>
<td>98</td>
<td></td>
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<tr>
<td><strong>Vt (L)</strong></td>
<td>0.55</td>
<td>0.93</td>
<td>1.41</td>
<td></td>
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<tr>
<td><strong>RR (br/min)</strong></td>
<td>13</td>
<td>21</td>
<td>40</td>
<td></td>
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<tr>
<td><strong>VE (L/Min)</strong></td>
<td>7.31</td>
<td>19.66</td>
<td>57</td>
<td>50%</td>
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<tr>
<td><strong>Vd/Vt</strong></td>
<td>0.17</td>
<td>0.15</td>
<td>0.12</td>
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<tr>
<td><strong>VO₂ (ml/kg/min)</strong></td>
<td>2.8</td>
<td>7.5</td>
<td>15</td>
<td>68%</td>
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<tr>
<td><strong>VO₂ (ml/min)</strong></td>
<td>196</td>
<td>523</td>
<td>1038</td>
<td></td>
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<tr>
<td><strong>VCO₂ (ml/min)</strong></td>
<td>183</td>
<td>523</td>
<td>1461</td>
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<tr>
<td><strong>RER</strong></td>
<td>0.94</td>
<td>0.96</td>
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<td><strong>METS</strong></td>
<td>1</td>
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<td><strong>HR (bpm)</strong></td>
<td>70</td>
<td>163</td>
<td>97%</td>
<td>97%</td>
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<tr>
<td><strong>O₂ Pulse</strong></td>
<td>3</td>
<td>5</td>
<td>7</td>
<td></td>
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<tr>
<td><strong>VE/VO2</strong></td>
<td>37</td>
<td>38</td>
<td>55</td>
<td>68%</td>
</tr>
<tr>
<td><strong>VE/VCO2</strong></td>
<td>40</td>
<td>39</td>
<td>39</td>
<td></td>
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<tr>
<td><strong>PET O2 (mm Hg)</strong></td>
<td>109</td>
<td>111</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td><strong>PET CO2 (mm Hg)</strong></td>
<td>32</td>
<td>31</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td>116</td>
<td>150</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td>64</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td><strong>SpO2</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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Simultaneous hemodynamics during the CPET confirm exercise precapillary pulmonary hypertension consistent with "Exercise PAH"

<table>
<thead>
<tr>
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<th>Rest</th>
<th>Peak VO\textsubscript{2}</th>
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<tbody>
<tr>
<td>RAP</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>PAP (Systolic/Diastolic/Mean)</td>
<td>40/18/25</td>
<td>90/35/53</td>
</tr>
<tr>
<td>CO/CI</td>
<td>3.7/2.1</td>
<td>9.3/5.3</td>
</tr>
<tr>
<td>PAOP</td>
<td>9</td>
<td>14</td>
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<tr>
<td>HR</td>
<td>70</td>
<td>163</td>
</tr>
<tr>
<td>BP</td>
<td>116/64</td>
<td>150/90</td>
</tr>
<tr>
<td>SpO\textsubscript{2}</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SV (ml)f</td>
<td>52</td>
<td>87</td>
</tr>
</tbody>
</table>
PAH Workup Involves an Obligate V/Q Scan

Ventilation  Perfusion
Angiograms

Right

Left
SPECTRAL CT Images

Z- Images

CT Fusion with Spectral Perfusion

Images courtesy A Gupta MD
Diagnosis: Mimic of CTEPH, Sarcoid Related PA Compression - > Exercise PH