Lessons From An Advanced Dyspnea Center: New Approaches to An Old Problem

Robert Schilz DO, PhD
Conflict of Interest Statement

• Robert Schilz DO, PhD
  – No conflicts relevant to this talk
Introduction, Definitions, Background
Objectives

• List current causes of "difficult to diagnose" chronic dyspnea
• Review standard evaluation of the dyspneic patient
• Discuss advanced imaging, exercise and cardiopulmonary testing available
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

Neuropsychological Components of Dyspnea

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). The larger circle labeled “D” shows the area activated by dyspnea (Banzett et al. 2000).

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

Exercise Training Decreases Dyspnea and the Distress and Anxiety Associated With It*

Monitoring Alone May Be as Effective as Coaching

Virginia Carrieri-Kohlman, DNSc, RN; Jenny M. Gormley, MSN, RN; Marilyn K. Douglas, DNSc, RN; Steven M. Paul, PhD; and Michael S. Stulbarg, MD

![Graph showing VAS (mm) for WOB, SOB, DD, DA]

**Figure 2.** Dyspnea components at isostage during treadmill ST at T1 and T2 for ME (n=27) and CE (n=24) groups. Isostage was the same stage during ST at T2 as that of the maximum stage achieved during ST at T1. Asterisk indicates p<0.01; two asterisks, p<0.001.
Traditional Approach to the Patient with Chronic Dyspnea
Typical Stepwise Evaluation in Dyspnea

Initial Evaluation
- Exam
- Testing

Review
- If secure diagnosis
- treat/refer for treatment

Refer
- Cardiology
- Pulmonary
Typical Dyspnea Evaluation and Differential Diagnosis
Typical Argument Among Consultants: Is It The Heart or the Lungs?
Typical Outcome of the Process

Refer → Evaluation → Review
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
Differential Diagnosis of Chronic Dyspnea

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# Differential Diagnosis of Chronic Dyspnea

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>Peripheral</th>
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<tbody>
<tr>
<td>Coronary Ischemia</td>
<td>Obstructive lung dz (COPD, asthma, chronic bronchitis)</td>
<td>Mitochondrial myopathy</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Interstitial lung dz</td>
<td>Muscular dystrophy</td>
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<tr>
<td>Atrial Fibrillation</td>
<td>Lung cancer</td>
<td>Phrenic nerve palsy</td>
</tr>
<tr>
<td>Valvular Heart Disease (AS, MR, MS)</td>
<td>Pulmonary HTN</td>
<td>Anemia, acidemia, hyperthyroidism</td>
</tr>
<tr>
<td>Congenital Heart Dz</td>
<td>Chest wall deformity, upper airway dysfunction, vocal cord dysfunction</td>
<td>Obesity, deconditioning</td>
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<tr>
<td>Step 1 – Initial assessment</td>
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<tr>
<td>History and physical examination</td>
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<tr>
<td>Chest radiography</td>
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<tr>
<td>Spirometry</td>
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<td>Pulse oximetry</td>
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<tr>
<th>Step 2 – Focused testing</th>
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<tr>
<td>Bronchoprovocation challenge testing</td>
</tr>
<tr>
<td>Electrocardiography</td>
</tr>
<tr>
<td>Further pulmonary function testing in older persons and high-risk groups</td>
</tr>
<tr>
<td>Laboratory tests: hemoglobin measurement, thyroid function tests, and renal panel in high-risk groups</td>
</tr>
<tr>
<td>Laryngoscopy if clinical history or flow-volume loop suggests vocal cord dysfunction</td>
</tr>
<tr>
<td>CT and/or bronchoscopy if chest radiograph is abnormal</td>
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</tbody>
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<tr>
<th>Step 3 – Cardiopulmonary exercise testing (CPET)</th>
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<tr>
<td>Determine the exercise response pattern</td>
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<tr>
<th>Step 4 – Specialized tests (or additional steps) based on CPET results</th>
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<tbody>
<tr>
<td>Normal</td>
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<tr>
<td>Reassurance</td>
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<tr>
<td>Gastroesophageal reflux evaluation and treatment</td>
</tr>
<tr>
<td>Psychiatric evaluation</td>
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<tr>
<td>Hyperventilation/psychogenic</td>
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<tr>
<td>Behavioral therapy</td>
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<tr>
<td>Psychiatric evaluation and treatment</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Weight loss and exercise training program</td>
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<tr>
<td>Cardiac/ischemia</td>
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<tr>
<td>Cardiac functional assessment</td>
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<tr>
<td>Cardiac catheterization</td>
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<tr>
<td>Cardiac pattern with gas exchange abnormalities; evaluation for pulmonary vascular disease if gas exchange abnormalities are present</td>
</tr>
<tr>
<td>Cardiac/deconditioning</td>
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<tr>
<td>Echocardiography, cardiac functional assessment</td>
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<tr>
<td>Exercise training program</td>
</tr>
<tr>
<td>Muscle biopsy</td>
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<tr>
<td>Pulmonary</td>
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<tr>
<td>Obstructive lung disease: treatment</td>
</tr>
<tr>
<td>Interstitial lung disease: high-resolution CT, lung biopsy</td>
</tr>
</tbody>
</table>

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
Problems with this Approach

• No accounting for layers of referral
• No accounting for difficulties in some diagnoses
  – HFPEF
  – Pulmonary Arterial Hypertension
  – Vocal Cord Dysfunction
• No accounting for diversions of diagnoses due to comorbidities
Alternate Practical Approach to the Evaluation of Dyspnea

Initial Evaluation
- Exam
- Testing

Review
- If secure diagnosis, treat/refer for treatment.
- If treatment fails, consider referral for re-evaluation

Refer
- Advanced Dyspnea Center
Initial Evaluation of Chronic Cryptogenic Dyspnea

• Level I
  – History and Physical Exam
  – Pulse Oximetry, Spirometry
  – Chest Radiography

• Level II
  – EKG
  – Lab: CBC, Thyroid Function, Electrolytes and Hepatic and Renal Function
  – CT Scanning

• Level IV
  – Echocardiography
Initial Evaluation of Chronic Cryptogenic Dypsnea

• Level I
  – History and Physical Exam
  – Pulse Oximetry, Spirometry
  – Chest Radiography

• Level II
  – EKG
  – Lab: CBC, Thyroid Function, Electrolytes and Hepatic and Renal Function
  – CT Scanning

• Level IV
  – Echocardiography

*Caveat: Tests are performed at rest!
Dyspnea Center Approach to the Patient with Chronic Dyspnea
Dyspnea Thinking process

System Approach

Pathophysiology

- CNS control
- Sensor
- Drive
- Medullary

- Respiratory Muscle
- Nasal and oral cavity
- Oropharynx
- Larynx
- Vocal cord
- Trachea
- Bronchus and bronchial tree
- Atelectasis
- Bronchial artery

- Ventilation
- Airway
- O2

- Oxygenation
- Intersitial vessel
- Right heart
- Pul. Artery
- Pulmonary capillary
- Pul. vein
- Left heart

- Systemic Delivery and perfusion
- Heart rate
- Stroke volume
- Preload
- Contractility
- Afterload

- Cardiac output
- SaO2
- Ventilation
- Oxygenation

Neuropsychiatry
Cardiovascular
Respiratory
Hematology
Metabolism/Endocrine
Our Approach To The Patient with Chronic Cryptogenic Dyspnea – Initial Testing and Review

- History and physical
- EKG
- Echocardiogram
- CXR/CT scan
- Spirometry, pulse oximetry rest and ambulatory
- Cardiopulmonary exercise testing
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
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?

¹Parshall, AJRCCM 2012:185;435
Non-Invasive Cardiopulmonary Exercise Testing
Cardiopulmonary Exercise Test (CPET)

http://www.medgraphics.com/download/UltimaCardiO2_4pg_060105-001rA.pdf
Exercise is the ideal stimulus

Balady, Circ 2010:122;191
### Common Variables Measured During CPX

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_2$ Peak (O$_2$ ml/kg/min)</td>
<td>Highest demonstrable VO$_2$</td>
<td>Expression of aerobic exercise capacity</td>
</tr>
<tr>
<td>VT (O$_2$ ml/kg/min)</td>
<td>VO$_2$ at which there is an accelerated rise in VE &amp; VCO$_2$ relative to VO$_2$</td>
<td>Measure of fitness (usually about 50-65% of VO$_2$ Max)</td>
</tr>
<tr>
<td>RER (VCO$_2$ / VO$_2$)</td>
<td>Ratio at max exercise</td>
<td>Indicator of subject effort (RER &gt;1.10)</td>
</tr>
<tr>
<td>VE / VCO$_2$ (Ventilatory efficiency) (VE = minute ventilation)</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 (VO$_2$/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
$\text{VO}_2$ Peak Declines with Age

Wasserman Principles of Exercise Testing & Interpretation 3$^{rd}$ Ed. 1999: p. 145
Determination of Anaerobic Threshold
(Beaver & Wasserman)

Beaver J Appl Physiol 1986:60;2020
Ventilatory Efficiency (VE/VCO₂)

Figure 2. Examples of the VE/VCO₂ slope during exercise. Three different slopes are shown with their respective values. In patients with heart failure, chronic obstructive pulmonary disease, and pulmonary hypertension, disease severity continues to increase as VE/VCO₂ response extends beyond the normal threshold (i.e., <30), with values >60 being reported. See text for details.

Balady, Circ. 2010;122:191-225
Variables on CPET that suggest cardiac vs pulmonary exercise limitation

<table>
<thead>
<tr>
<th>Findings to suggest cardiac cause</th>
<th>Findings to suggest pulmonary cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low “oxygen pulse” (VO2/HR) a surrogate of stroke volume</td>
<td>Reduced breathing reserve (&lt; 15%)</td>
</tr>
<tr>
<td>ECG changes indicative of ischemia</td>
<td>Arterial desaturation (pulse oximetry)</td>
</tr>
<tr>
<td>Blunted or decreased HR or BP response to exercise</td>
<td>Elevated VE/VCO2 ratio</td>
</tr>
</tbody>
</table>
Diagnostic Patterns of Abnormal CPET Results

Illustration of the physiologic adaptation from rest to maximal aerobic exercise.

- Resting State
  \[ \text{VO}_2 \leq 3.5 \text{ mLO}_{2} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \]

- Aerobic Exercise Progressed to Maximum Tolerance
  - Pulmonary:
    - Increase in respiratory rate and tidal volume
    - Increase in minute ventilation
    - Increased intake of oxygen and removal of carbon dioxide
  - Cardiac:
    - Increase in heart rate
    - Increase in stroke volume
    - Increase in cardiac output
  - Peripheral:
    - Increase in oxygen extraction for energy production within mitochondria
    - Widening of a-vO\textsubscript{2} diff

- Maximal Aerobic Exercise Tolerance
  \[ \text{VO}_2 = 20-55 \text{ mLO}_{2} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \]
  in apparently healthy subjects. Value achieved dependent upon age, gender, fitness level and genetic predisposition.
Exercise Echo Testing
What Does DHF Look Like On Echo?

Nagueh. JASE, 2009.

Normal 35 years old

Hypertension with LVH 58 years old
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
I-CPET Allows for Hemodynamic Phenotyping

- Peak Exercise mean PAP and LAP (via PCWP)
- Peak Exercise mixed venous O2 saturation
- Δ CaO$_2$ – CvO$_2$ gradient
- Fick Cardiac Output
- Pulmonary Vascular Resistance: PVR = (mPAP – LAP)/CO
- Δ mPAP (mm Hg) / Δ Cardiac Output (L/min)
Exercise-Induced Pulmonary Arterial Hypertension

James J. Tolle, MD; Aaron B. Waxman, MD, PhD; Teresa L. Van Horn, BA; Paul P. Pappagianopoulos, MEd; David M. Systrom, MD

CPET Diagnoses

- 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

(Chart showing CPET Diagnoses: PVH 48%, PAH 23%, Peripheral 14%, Other 11%, Normal 4%)

Tolle, Circulation 2008;118:2183
PA pressure normal response to exercise

Lewis, Circ 2013:128;1470
Pulmonary Circulation Pressure-Volume Response to Exercise

Lewis, Circ 2013:128;1470
A diagnostic algorithm for interpreting iCPET results.

Diagnostic Framework for elevated PA pressure in Heart Failure

Pulmonary Hypertension (mPAP > 25 mmHg)

PCWP ≤ 15 mmHg

PCWP > 15 mmHg

Is PVR or TPG Elevated?

NO

“PASSIVE PH”

YES

“MIXED PH”

Does PVR Decline with Reduction in PCWP?

NO

“FIXED PH”

YES

“REACTIVE PH”

Consider exercise, volume challenge, or vasodilator response to refine the hemodynamic classification

Lewis, Circ HF 2011:4;541
Exercise Hemodynamics of HFpEF

Borland, BA et al. Circ Heart Fail. 2010 Sep;3(5):588-95
UH Dyspnea Program, Summary and Conclusions
Alternate Approach to Cardiopulmonary Dysfunction

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

• 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 the preferred stressor to differentiate cardiac and pulmonary causes.
• In patients with both heart and lung disease, invasive cardiopulmonary exercise allows for determining which is predominant.
• Preliminary data suggests that exercise prescription based on testing and application of modern exercise training strategies may improve performance in the setting of difficult to manage cardiopulmonary disease.
Dyspnea Center

Referral Lines: 216-844-3800 or 216-844-2639