The Evaluation of Cough in the Pulmonary Function Laboratory

Katrina M. Hynes, MHA, RRT, RPFT
Supervisor, Mayo Clinic Pulmonary Function Lab
AARC Diagnostic Section Chair
Background
Chronic Cough

• Definition: A cough that persists beyond 8 weeks
• Symptom-based problem
• Requires further diagnostic evaluation
• Social impact
  • Anxiety
  • Physical discomfort
  • Social and personal embarrassment
  • Reduction in quality of life

Chronic Cough 1

Prevalence, pathogenesis, and causes of chronic cough

Lancet 317 1364-74, 2008
Background

Prevalence of cough?

- Cross-sectional survey of 36 general practices.
  - 4003 Subjects
  - Prevalence of chronic cough was 12%
  - Severe 7%

Thorax 2006;61:975–979.
Background
Causes of Chronic Cough

• Infectious
• Airways disorders
• Lung parenchymal disease
• Tumors
• Irritation of the external auditory meatus
• Upper airway cough syndrome (UACS)
• Esophageal causes (GERD)
• Drugs (ACE inhibitors and β-blockers)
• Airway irritants
Clinical Practice Guidelines

70-90% of cases seen in clinical practice
- Upper airway cough syndrome (UACS)
- GERD
- Asthma

January 2006; 129(1_suppl) Diagnosis and Management of Cough: ACCP Evidence-Based Clinical Practice Guidelines
Evaluation of Chronic Cough in the Pulmonary Function Lab

- 43 staff
- 24 procedure rooms
- 150-250 patients/day
Evaluation of Chronic Cough

Spirometry

- **Spirometry** (meaning *the measuring of breath*) is the most common pulmonary function test (PFTs)
Spirometry and the Obstructive pattern

- Asthma
- Chronic Bronchitis
- Emphysema
Spirometry and the Restrictive pattern

- Intrinsic lung disease
  - IPF, sarcoidosis, etc.
- Extra-pulmonary
  - Pneumothorax, pleural effusion, etc.
- Neuromuscular
  - ALS, myasthenia gravis etc.
- Chest wall: obesity, scoliosis, kyphosis
Spirometry Utilization and Other Procedures
ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests

Allan L. Coates¹, Jack Wanger², Donald W. Cockcroft³, Bruce H. Culver⁴ and the Bronchoprovocation Testing Task Force: Kai-Håkon Carlsen⁵,

Published in ERJ in 2017
Evaluation of Chronic Cough
Bronchial Provocation - Guidelines

• So what happened to Exercise, EVH, Mannitol?

Indirect Bronchoprovocation accepted for publication at the time of slide deadline
Evaluation of Chronic Cough
Bronchial Provocation - Guidelines

  • www.thoracic.org
Challenge Testing

Direct stimulus – Methacholine Challenge

Effector cells
• Airway smooth muscle cells
• Bronchial endothelial cells
• Mucus producing cells

Indirect stimulus – Mannitol/Exercise

Intermediary cells
• Inflammatory cells

Airflow limitation
Methacholine Challenge Test

- **Methacholine chloride** is a parasympathomimetic (cholinergic) bronchoconstrictor agent
- Methacholine is derived from acetylcholine, a naturally occurring substance in the body, and can cause the airways to tighten and swell, in sensitive people.
- FDA-approved methacholine
  - Provocholine®
Methacholine Test Methodology
Protocols

• Five-breath dosimeter protocol (No TLC)
• Tidal breathing dosing protocol (recommended)
## 2017 “ERS” Bronchial Challenge Guideline

### TABLE 4 Example of doses using the English Wright nebuliser for 2 min

<table>
<thead>
<tr>
<th>Doubling increments</th>
<th>Quadrupling increments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentration mg·mL(^{-1})</strong></td>
<td><strong>Dose µg</strong></td>
</tr>
<tr>
<td>0.0625</td>
<td>1.425</td>
</tr>
<tr>
<td>0.125</td>
<td>2.969</td>
</tr>
<tr>
<td>0.25</td>
<td>5.938</td>
</tr>
<tr>
<td>1</td>
<td>23.75</td>
</tr>
<tr>
<td>2</td>
<td>47.5</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>190</td>
</tr>
</tbody>
</table>

Shown are the incremental doses at specific concentrations for both doubling and quadrupling increments.
Methacholine Challenge Test

- Example:
  - Baseline FEV1 4.0L
  - Control (diluent) 3.75L
  - $3.75 \times 0.8 = 3.0L$
  - $3.75 \times 0.9 = 3.38L$
  - $PD_{20} = 3.00L$

# Methacholine Challenge Test Interpretation

<table>
<thead>
<tr>
<th>Categorization of Airway Response to Methacholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD$_{20}$ (µmole)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>&gt; 2.0</td>
</tr>
<tr>
<td>0.5-2.0</td>
</tr>
<tr>
<td>0.125-0.5</td>
</tr>
<tr>
<td>0.03-0.125</td>
</tr>
<tr>
<td>0.008-0.03</td>
</tr>
</tbody>
</table>
Mannitol Challenge Test

- **Indirect** and osmotic stimulant
  - Increases osmolarity of airway surface liquid
  - Release of inflammatory mediators from mast cells and basophils (e.g. leukotriene)
- Sugar alcohol, dry powder (stored below 25°C)
- Utilizes a special dry-powder inhaler (DPI)
- No diluent or nebulization required
- Will be reintroduced into the US market by Methapharm
Mannitol Challenge Test

- Aridol Kit
  - Aridol capsules (mannitol)
  - 1 empty capsule
  - Osmohaler inhaler device (DPI)
Mannitol Challenge Procedure

**Dosing scheme**

- Total maximum dose = 635 mg
Mannitol Challenge Test

Procedure

• Pre-challenge spirometry
  • FEV₁ at least 60% of predicted

• Administer mannitol using Osmohaler

• At 60 seconds perform spirometry
Mannitol Challenge Test

Procedure

• Perform 3 acceptable, 2 repeatable FVC maneuvers (according to ATS/ERS Guidelines). Use the higher of these two values to calculate the change in FEV₁

• If Baseline FEV₁ is >10% lower than pre-challenge FEV₁ - stop challenge

• Calculate target FEV₁
  • highest Baseline value * 0.85

• Continue with subsequent dosages
Mannitol Challenge Test

**Reporting results**

- **PD$_{15}$** - 2 decimal places in mg/mL (e.g., 33.85 mg)

- 15% decline in FEV1 is a **positive test**
  - If no 15% fall in FEV$_1$ after highest dose, PD$_{15}$ reported as greater than 635 mg (**negative test**)

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Evaluation of Chronic Cough

Exhaled Nitric Oxide

• Numerous biomarkers of inflammation that have been detected in exhaled breath

Analysis of exhaled breath condensate in respiratory medicine: methodological aspects and potential clinical applications

Paolo Montuschi

Therapeutic Advances in Resp Disease 2007 1;5
Exhaled Nitric Oxide Guidelines

- 2005 ATS+ERS (www.thoracic.org)
  
American Thoracic Society Documents

ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005

- 2011 ATS Interpretation

An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications

Raed A. Dweik¹,², Peter B. Boggs³, Serpil C. Erzurum¹,², Charles G. Irvin⁴, Margaret W. Leigh⁵, Jon O. Lundberg⁶, Anna-Carin Olin⁷, Alan L. Plummer⁸, D. Robin Taylor, on behalf of the American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications

This Official Clinical Practice Guideline of the American Thoracic Society (ATS) was approved by the ATS Board of Directors, May 2011

Exhaled Nitric Oxide

- $eNO = F_{E_{NO}}$*

- $eNO$ is an index of eosinophilic (allergic) airway inflammation.

- $eNO$ is *not* increased with bronchospasm.

* The abbreviation for fraction of exhaled nitric oxide at a flow of 50mL/sec
Exhaled Nitric Oxide Prolonged Cough

- 71 pts c/o prolonged cough
  - Bronchial asthma (30)
  - Cough variant asthma (18)
  - Bronchitis (8)
  - Others (15)

- Conclusion: FeNO could be used as a diagnostic marker of prolonged cough, especially for the differential diagnosis BA and CVA from EB and others.

Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough

Suguru Sato*, Junpei Saito, Yasuko Sato, Taeko Ishii, Wang Xintao, Yoshinori Tanino, Takashi Ishida, Mitsuru Munakata

Respiratory Medicine (2008) 102, 1452e1459
Exhaled Nitric Oxide
Instrumentation

• Circassia Niox Vero
  • Electrochemical
  • Hand-held
  • Oral only
Exhaled Nitric Oxide “Indications”

• **Diagnosis**
  – Diagnose eosinophilic airway inflammation
  – Support the diagnosis of asthma when objective evidence is lacking
  – Help determine when respiratory symptoms are not due to asthma
  – Determine whether uncontrolled allergic airway inflammation is contributing to poor asthma control

• **Aid in Treatment and Monitoring**
  – Determine the likelihood of steroid responsiveness
  – Establish baseline FeNO level during a period of clinical stability, which can be subsequently monitored
  – Help determine whether patients are adhering to prescribed corticosteroid treatment
Exhaled Nitric Oxide Technique

• Pretest instructions
  • Refrain from eating, drinking, smoking, and exercise for 1 hour before test
• Record the time of last bronchodilator administration
• Testing: Follow vendor specific testing instructions

American Thoracic Society Documents

ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005
Exhaled Nitric Oxide: Results

- Low FENO less than 25 ppb (20 ppb in children) be used to indicate that eosinophilic inflammation is unlikely.
- FENO greater than 50 ppb (35 ppb in children) be used to indicate that eosinophilic inflammation.
- FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously.
Evaluation of Chronic Cough
Rhinoscopy

• Flexible rhinoscopy is a quick, office-based procedure used to examine the entire nasal cavity

• Can be used in the evaluation Upper airway cough syndrome (UACS)
Evaluation of Chronic Cough
24 Hour Laryngopharyngeal pH monitoring
Evaluation of Chronic Cough
24 Hour Laryngopharyngeal pH monitoring

• Gastroesophageal Reflux Disease (GERD).
  • Classic symptom: burning sensation in your lower chest (heartburn).
  • Major cause of chronic cough
  • GERD may lead to Barrett’s esophagus, a type of intestinal metaplasia\(^1\) which is a precursor for carcinoma

• Laryngopharyngeal reflux (LPR) is similar to GERD
  • Does not have the classic symptoms of GERD
Evaluation of Chronic Cough

24 Hour Laryngopharyngeal pH monitoring

- Laryngopharyngeal reflux (LPR) is sometimes termed “Silent reflux”
- Common symptoms:
  - Excessive throat clearing, sore throat
  - Persistent cough
  - Hoarseness
  - A "lump" in the throat that doesn't go away with repeated swallowing
Evaluation of Chronic Cough
24 Hour Laryngopharyngeal pH monitoring

• New Diagnostic/Monitoring Technology

• pH measurement system revolutionizes pH testing.

• Technology uniquely capable of sensing and recording both aerosolized and liquid pH levels allows for less invasive placement
Evaluation of Chronic Cough
24 Hour Laryngopharyngeal pH monitoring

- Off PPI or H2blocker for 10 days prior to study
- System uses small catheter introduced via the naris and placed just behind/beside the uvula for the study
- Data collected via a transmitter that transfers to a recorder
Oropharyngeal pH Monitoring for the Detection of Liquid and Aerosolized Supraesophageal Gastric Reflux

Journal of Voice, Vol. 23, No. 4, 2009

**TABLE 3.**
Characteristics of the 48 Dx-Reflux Events

<table>
<thead>
<tr>
<th>pH Sensor</th>
<th>AR (pH&lt;4) (acid reflux)</th>
<th>WAR (pH 4–7) (weakly acid reflux)</th>
<th>Median pH (25–75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx</td>
<td>(n=3) 6.25% Median pH 3.5 25–75% [3.5–3.8]</td>
<td>(n=45) 93.75% Median pH 5.75 25–75% [5.1–6.3]</td>
<td>5.6 (5.0–6.2)</td>
</tr>
<tr>
<td>Pharynx (P)</td>
<td>(n=12) 25% Median pH 3.9 25–75% [3.8–4.0]</td>
<td>(n=36) 75% Median pH 5.75 25–75% [4.8–6.4]</td>
<td>5.2 (4.1–6.2)</td>
</tr>
<tr>
<td>5 cm &gt; LES (LES)</td>
<td>(n=32) 66.67% Median pH 2.8 25–75% [2.2–3.1]</td>
<td>(n=16) 33.33% Median pH 5.4 25–75% [4.4–6.2]</td>
<td>3.1 (2.5–4.3)</td>
</tr>
</tbody>
</table>
Hoarseness and chronic cough: Would you suspect reflux?

<table>
<thead>
<tr>
<th>Finding</th>
<th>Frequency among patients with LPRD (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphonia/hoarseness (intermittent)</td>
<td>71</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>51</td>
</tr>
<tr>
<td>Globus pharyngeus</td>
<td>47</td>
</tr>
<tr>
<td>Chronic throat clearing</td>
<td>42</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>35</td>
</tr>
<tr>
<td>Heartburn</td>
<td>35</td>
</tr>
</tbody>
</table>

*The frequency of other symptoms associated with LPRD is not known.
Pediatric cough is a common complaint in 35% of preschool children and 9% of 7–11-year-olds.

Laryngopharyngeal reflux
Otolaryngologists are familiar with gastroesophageal reflux disease (GERD) but prefer to use the term laryngopharyngeal reflux (LPR) to refer to extraesophageal manifestations. Cough as well as asthma exacer-
Case 1

- 26 yo female referred for multiple pulmonary nodules and chronic cough
  - #1 *Multiple pulmonary nodules*
    - r/o histoplasmosis.
    - PPD negative.
    - Pet exposure (kitty litter boxes, toxocara as well as toxoplasma).
  - #2 *Increasing cough*
    - The possibility of reflux is very strong.
  - #3 *Suspect obstructive sleep apnea*
Case 1

- Histoplasmosis – negative

- Toxocara Antibody - POSITIVE
  - This indicates exposure to the and does not necessarily mean those nodules are active Toxocara infection. Toxocariasis is a human illness caused by immature parasite worms of either the dog roundworm (Toxocara canis) or the cat roundworm (Toxocara cati).

- Chronic cough and dental erosion
  - 24 Hour Laryngopharyngageal pH monitoring
Case 1
24 Hour Laryngopharyngeal pH monitoring

<table>
<thead>
<tr>
<th>Age: 26</th>
<th>Gender: Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm): 160.5</td>
<td>Weight (kg): 139.3</td>
</tr>
<tr>
<td>Total Procedure Time: 18:15:00</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Time Below Baseline</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>&lt;0.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Episodes</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>&lt;1.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Longest Episode</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>&lt;0.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RYAN Score</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.12</td>
<td>&lt;9.41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supine pH &lt; 5.0</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16.94</td>
<td>&lt;5.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Episodes</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>162</td>
<td>&lt;4.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Longest Episode</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21.88</td>
<td>&lt;16.97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RYAN Score</th>
<th>Patient’s Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>124.79</td>
<td>&lt;6.80</td>
</tr>
</tbody>
</table>

Minimum pH: 4.34  Maximum pH: 6.98  Median pH: 5.95
Variance: 0.40   Standard Deviation: 0.64   Arithmetic Mean: 5.84
Evaluation of Chronic Cough

Mayo Clinic’s Clinical Flowchart


FIGURE. Evaluation and management of chronic cough. ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CXR = chest x-ray; ENT = ear, nose, and throat or otolaryngology; GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflex; NAEB = nonasthmatic eosinophilic bronchitis; UACS = upper airway cough syndrome.
Questions & Discussion