Cough Pathophysiology: Upper Airway Perspective (Including Idiopathic Cough):
Is it Laryngeal Hypersensitivity?

Ron Balkissoon MD MSC FRCP C
National Jewish Health
Denver
## Conflict of Interest

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Relationship</th>
<th>Topics</th>
<th>Payment</th>
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<td>Astra Zeneca</td>
<td>Speaker’s Bureau Advisory Board Manuscript Review</td>
<td>COPD/Asthma</td>
<td>Honoraria None</td>
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<td>Forest</td>
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## Major Causes of Cough

<table>
<thead>
<tr>
<th>Authors</th>
<th>year</th>
<th># Patients</th>
<th>PND/BA/GERD (%)</th>
<th>EB (%)</th>
<th>PI (%)</th>
<th>CB (%)</th>
<th>Misc or No Dx (%)</th>
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<td>49</td>
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<td>Palombini et al</td>
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<td>Ayik et al</td>
<td>2003</td>
<td>39</td>
<td>44</td>
<td>31</td>
<td>5</td>
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<td>20</td>
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Upper Airway Causes of Cough

Upper Airway Cough Syndrome: Formerly known as Post Nasal Drip

Sinonasal disease
- Hyperplastic nasal polyps
- Samter triad
- Stubborn bacterial overgrowth
- Fungal disease
- Distorted anatomy
- Post-surgical phenomena
  - Retained uncinate process
  - Caldwell-Luc antrostomies and mucus recirculation
  - Surgical failure to reopen natural sinus ostia
Upper Airway Causes of Cough

• Regional neurologic reflex/pathology
  – Arnold’s nerve/reflex from External Auditory Canal Foreign Body

• Direct contact irritation
  – Sinonasal mucus
  – Inhalant or ingestion allergens
  – Chronic laryngitis
    • Infectious
    • Inflammatory
    • Neoplastic
Surgical Failure

Acute maxillary sinusitis, CT imaging
Sensory nerve receptors

Superior laryngeal n.

±Cortical processing

Nucleus Ambigus (Medulla)

Recurrent laryngeal n.

Afferent

Efferent

Vagus Nerves

Superior Laryngeal Nerve

Reccurrent Laryngeal Nerve

Cough Reflex

Courtesy of Boyd Jacobson
Pathophysiology of Cough

• Cough is a protective reflex to minimize lung injury from potentially noxious material(s)

• The larynx is the gateway/gatekeeper to the lungs
The Nose is the Lungs HVAC System

• **Heating:**

• **Ventilation:** Air conduction

• **Air Conditioning:**
  – Humidification
  – Filtration

• **Warning System (Olfaction)**
Afferent Cough Receptors
Rapidly Adapting Receptors in Mucosal Lining

- Ear
- Nose
- Oropharynx
- Larynx
- Trachea and large central bronchi
- Esophagus
- Pericardium
- Diaphragm
- Stomach
“Laryngeal” Sensory Receptors

Cough Receptors:
• Myelinated rapidly adapting irritant receptors
• Non myelinated slowly adapting C fibers

Afferent Nerves- trigeminal, glossopharyngeal, superior laryngeal or vagus n.
Laryngeal Sensory Receptors

Chemoreceptors:
- Water
- Ammonia
- CO2, SO2
- Cigarette smoke
- milk, gastric content

Mechanoreceptors:
- Pressure (touch)
- Flow (flow, cooling)
- Proprioception
- Drive (laryngeal muscle contraction)
Laryngeal Sensory Receptors

• Irritant receptors
  – Nociceptive C fibers
  – G-Protein coupled receptors (GPCR)
  – Transient receptor potential vanilloid (TRPV-1)
  – Transient receptor potential ankyrin 1 (TRPA-1)
Upper Airway Cough Syndrome

- TRPV-1 activation → burning sensation
- TRPA-1 activation → burning cold sensation
- Other C-fiber neurons have H-1 receptors that lead to sensation of itch.

Activation of Nociceptors in Trachea

A

GPCR Agonists eg. Bradykinin

\[ \text{Inhaled and endogenous irritants} \]

TRPV1

TRPA1

\[
\text{outside} \quad \text{inside}
\]

\[ \text{Signal transduction pathways} \]

\[ \text{GENERATOR POTENTIAL} \]

\[ \text{Na} \]

\[ \text{K} \]

\[ \text{ACTION POTENTIALS} \]

B

Undem B J, Carr M J. Chest 2010;137:177-184
Hypersensitivity of Laryngeal C-Fibers Induced by Volatile Anesthetics in Young Guinea Pigs
(Mutoh et al AJRCCM 2003)

Background:
• Children develop laryngospasm, cough, upper airway obstruction following halothane anesthesia.
• Due to stimulation of laryngeal C- fibers?
• C fibers play important role in triggering airway reflexes
• 50% afferents in SLN are non-myelinated C fibers
Hypersensitivity of Laryngeal C-Fibers Induced by Volatile Anesthetics in Young Guinea Pigs
(Mutoh et al AJRCCM 2003)

Design:
1. Expose Guinea Pigs to inhaled Halothane
2. Dissect out laryngeal mucosal C-fiber neurons to test sensitivity to chemical (capsaicin) challenge and Mechanical (laryngeal hyperinflation) stimuli

Results:
• Halothane increased isolated C-fiber sensitivity to chemical (capsaicin) and mechanical (laryngeal hyperinflation) stimuli
Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease.

C5: concentration of aerosolized capsaicin solution that caused five coughs.
Extrathoracic and Intrathoracic Responsiveness in Sinusitis and VCD

• 106 patients with chronic rhinosinusitis treated with antibiotics and inhaled nasal steroids X 2 weeks

• Pre and post treatment histamine challenges
  bronchial hyperresponsiveness B-HR
  extrathoracic hyperresponsiveness EA-HR

• Nasal swabs and lavage
• Serum IgE/Rast

Bucca JACI 1995
RATIO OF EXPIRATORY TO INSPIRATORY FLOWS AT 50% OF THE VITAL CAPACITY

\[
\frac{\text{FEF}_{50}}{\text{FIF}_{50}} = 0.64
\]
Extrathoracic and Intrathoracic Responsiveness in Sinusitis and VCD

88 Patients Completed Study:

- EA-HR 76/88 (86%)
- (EA + B)-HR 46/88 (52%)

- Nasal Lavage and smears
  - neutrophilia 88 (100%)
  - eosinophilia 36 (41%)
Effect of treatment on pre-challenge lung function, bronchial and EA responsiveness, and neutrophil score in nasal lavage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before treatment (mean ± SEM)</th>
<th>After treatment (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV$_1$ (L)</strong></td>
<td>3.25 ± 0.09</td>
<td>3.26 ± 0.09</td>
</tr>
<tr>
<td><strong>MEF$_{50}$ (L/sec)</strong></td>
<td>4.36 ± 0.14</td>
<td>4.54 ± 0.15</td>
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<tr>
<td><strong>MIF$_{50}$ (L/sec)</strong></td>
<td>5.14 ± 0.15</td>
<td>5.60 ± 0.16</td>
</tr>
<tr>
<td><strong>PC$_{20}$ (mg/ml)</strong></td>
<td>7.94 ± 1.12</td>
<td>15.8 ± 1.10†</td>
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<tr>
<td>B-HR ($n$)</td>
<td>46 (52%)</td>
<td>17 (19%)†</td>
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<tr>
<td><strong>PC$<em>{25}$MIF$</em>{50}$ (mg/ml)</strong></td>
<td>3.24 ± 1.12</td>
<td>16.2 ± 1.10†</td>
</tr>
<tr>
<td>EA-HR ($n$)</td>
<td>76 (86%)</td>
<td>18 (20%)†</td>
</tr>
<tr>
<td>Neutrophil score ($n$)</td>
<td>3.08 ± 0.17</td>
<td>0.68 ± 0.84†</td>
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</table>

*Geometric mean. †$p < 0.001.$

Bucca JACI 1995
Extrathoracic airway (EA) and Intrathoracic Responsiveness in Sinusitis and VCD

Conclusions:
• Sinusitis leads to increased responsiveness in EA
• mediators from infected sinuses may seed inflammatory process to pharynx/larynx via PND
• may trigger a “pharyngo-bronchial” reflex
• mechanism of “pharyngo-bronchial” reflex remains unknown
Laryngopharyngeal Reflux (LPR)
GERD vs. LPR \(\Rightarrow\) Cough

- Distal (LES) vagus afferents may stimulate cough
  - Irwin et al demonstrate stronger correlation with distal pH probe sensor
- Supraglottic sensation more directly stimulates cough

Laryngopharyngeal findings & reflux

- Posterior-predominant supraglottic edema/erythema
- Glottic abnormalities
- Epiglottic malformations
- Posterior pharyngeal wall effects
- Lingual tonsillar hypertrophy
Laryngo-Pharyngeal Reflux (LPR)

Aryepiglottic fold edema and erythema

Posterior Commissure Thickening (pachyderma)

Posterior Cobblestoning
Laryngoscopic Features of LPR

- Posterior Cobblestoning
- Posterior Commissure Thickening
- Aryepiglottic Fold Thickening
Laryngeal Biopsy (Patient)

Nasopharyngeal Reflux
Posterior Cobblestoning

METHODS: Sixty-eight participants underwent 24-hour pH testing, chronic rhinosinusitis (CRS) patients symptomatic after endoscopic sinus surgery, CRS patients successfully treated by endoscopic sinus surgery, volunteers without a CRS history.

Assessment:
1. pH probes: nasopharyngeal (NP), laryngopharyngeal (LP), and distal esophageal sensors.
2. SNOT questionnaire
3. MRSI PND questionnaire

RESULTS:
- Positive correlation of $r = 0.87$ between SNOT-20 and MRSI PND items.
NPR < pH 4
  - no significant difference existed between participants with and without reflux on the SNOT-20 or MRSI ($p > 0.05$).
NPR < pH 5,
  - reflux-positive participants exhibited significantly more PND symptoms on the SNOT-20 ($p = 0.030$) and the MRSI ($p = 0.018$) compared with participants without reflux.
- Participants with LPR had significantly more PND symptomatology on the SNOT-20 ($p = 0.010$) versus those without LPR.

CONCLUSION: Objective evidence of NPR and LPR exists in patients reporting PND. Reflux treatment may reduce PND complaints.
Direct nasopharyngeal reflux of gastric acid is a contributing factor in refractory chronic Rhinosinusitis.

- 38 patients with previous endoscopic sinus surgery
- 76 vs 24% of CRS group had NPR (p=0.00003)
- pH < 5 greater number of events than pH<4

Linking laryngopharyngeal reflux to otitis media with effusion: pepsinogen study of adenoid tissue and middle ear fluid

METHODS:
Middle ear effusions (MEEs) and adenoidal tissue biopsies from:
1. patients undergoing tympanostomy tube placement and adenoidectomy
2. adenoid specimens were taken during adenoidectomy (+/- tonsillectomy) from children with no history of OME.

- adenoid tissues were analyzed immunohistochemically to confirm the presence of pepsinogen.
- MEE total pepsinogen levels were measured with enzyme-linked immunosorbent assay.

RESULTS:
- Adenoid tissue of the OME group (n = 25)
  - demonstrated significantly higher pepsinogen immunoreactivity when compared with the adenoid tissue of the control group (n = 29),
  - pepsinogen was detected in 84% of MEEs from the OME group,
  - concentrations 1.86 to 12.5 times higher than that of serum

CONCLUSION: LPR plays an important role in the pathogenesis of OME as gastric reflux reaches the middle ear through the nasopharynx and eustachian tube to cause OME.
ACE inhibitor Induced Cough

• Subjects with ACE inhibitor induced cough typically report a tickle or scratching sensation in throat

• Mechanism unknown however:
  – Bradykinin, substance P normally broken down by ACE therefore accumulate in upper airway and or lung in patients on ACE inhibitors
  – Bradykinin causes increase prostaglandin production
  – Bradykinin may induce increased sensitivity of laryngeal airways
  – Studies show increased sensitivity to Capsaicin challenge

Peter V. Dicpinigaitis, MD, FCCP
ACCP guidelines Chest 2006
Irritant Associated (Occupational) VCD
Irritant Associated VCD (IVCD)  
(Perkner et al JOEM 1998)

• Case Definition
  • irritant exposure
  • onset symptoms within 24 hours
  • no history of VCD or other laryngeal disease
  • Laryngoscopy confirmed VCD

• Compared 11 cases with 33 age matched control VCD cases
Most Common Exposure

NJC Experience

• Chlorine gas
• Ammonia
• Smoke from fires
Irritant Associated VCD (IVCD)

No significant difference found between IVCD and VCD

• Health care worker
• Psychiatric history
• Signs and symptoms:
  • *Chest pain more common in IVCD group
  • wheeze, cough, dyspnea, choking, stridor, voice changes
• Pulmonary function tests
  • $\text{FEV}_1/\text{FVC}$, $\text{FEF}_{50}/\text{FIF}_{50}$, Flow volume loop
Reactive Airways Dysfunction Syndrome (RADS) vs Vocal Cord Dysfunction (VCD): National Jewish Experience

• Review series of patients referred to Department of Environmental and Occupational Health Sciences at National Jewish Medical Research Center for evaluation of difficult to treat or atypical “RADS”

• 77 patients reviewed
Reactive Airways Dysfunction Syndrome (RADS) vs Vocal Cord Dysfunction (VCD): National Jewish Experience

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<th></th>
<th>GERD</th>
<th>PND</th>
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<tr>
<td>VCD alone</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>n = 12</td>
<td>(91%)</td>
<td>(66%)</td>
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<tr>
<td>RADS and VCD</td>
<td>37</td>
<td>42</td>
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<tr>
<td>N = 65</td>
<td>(56%)</td>
<td>(64%)</td>
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(Balkissoon R, Abstract, AJRCCM April Supplement 2000)
Hypothesized “Vicious Cycle”

Upper Respiratory Tract Infection/(Non)/Allergic rhinitis

Cough

GERD

Laryngopharyngeal Reflux

Nasopharyngeal Reflux

Chronic Cough

Habituated/Neuropathic Cough
Cough Habituation or Neuropathic cough: Neural Plastic Response to Repetitive Nocistimulation

depolarization → Stimulus → Neurotransmitter

Second messenger

mRNA fos

fos protein

C-fos

C-jun

Transcription of IE Genes

DNA binding

FOS JUN

Summary

• Cough is a protective reflex
• Neurologic Pathways for upper airway cough syndrome are complex
• Common causes of chronic cough all lead to laryngeal irritation
• Unified airway suggests lower airway disease may cause reflex sensations in throat that induce cough
• Neural plasticity may lead to lower threshold for cough reflex with chronic nociceptive input