Management of Functional Heartburn

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Consulting Albert on Functional Heartburn
Functional Esophageal Disorders

Rome III

Functional Esophageal Disorders

- Functional heartburn
- Functional chest pain of presumed esophageal origin
- Functional dysphagia
- Globus
Functional Heartburn (Rome III Criteria)

Must include all of the following criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:
Functional Heartburn
(Rome III Criteria)

Must include all of the following criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:

• Burning retrosternal discomfort or pain
Functional Heartburn
*(Rome III Criteria)*

Must include all of the following criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:

- Burning retrosternal discomfort or pain
- Absence of evidence that gastroesophageal reflux is the cause of the symptom
Functional Heartburn
(Rome III Criteria)

Must include all of the following criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:

- Burning retrosternal discomfort or pain
- Absence of evidence that gastroesophageal reflux is the cause of the symptom
- Absence of histopathology-based esophageal motility disorders
Functional Heartburn
*(Rome III Criteria)*

Must include all of the following criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:

- Burning retrosternal discomfort or pain
- Absence of evidence that gastroesophageal reflux is the cause of the symptom
- Absence of histopathology-based esophageal motility disorders
- *Patients with normal acid exposure and positive association of symptoms with reflux events (hypersensitive esophagus)*—Excluded
Functional Heartburn
(Rome III Criteria)

Must include all of the following criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:

• Burning retrosternal discomfort or pain
• Absence of evidence that gastroesophageal reflux is the cause of the symptom
• Absence of histopathology-based esophageal motility disorders
• Patients with normal acid exposure and positive association of symptoms with reflux events (hypersensitive esophagus)—Excluded
• Patients with normal acid exposure and negative symptom index who are responsive to PPI—Excluded
Who Falls Under the Category of Functional Heartburn?

Patient with heartburn

Who Falls Under the Category of Functional Heartburn?

Patient with heartburn

Endoscopy

Who Falls Under the Category of Functional Heartburn?

1. Patient with heartburn
2. Endoscopy
3. Normal endoscopy

Who Falls Under the Category of Functional Heartburn?

- Patient with heartburn
  - Endoscopy
    - Normal endoscopy
      - pH testing

Who Falls Under the Category of Functional Heartburn?

- Patient with heartburn
- Endoscopy
- Normal endoscopy
- pH testing

(50%) abnormal

NERD

Who Falls Under the Category of Functional Heartburn?

Patient with heartburn
Endoscopy
Normal endoscopy
pH testing

(50%) abnormal
(50%) normal

Symptom index

NERD

Who Falls Under the Category of Functional Heartburn?

- Patient with heartburn
  - Endoscopy
    - Normal endoscopy
      - pH testing
        - (50%) abnormal
          - Positive (37%)
            - NERD
          - Symptom index
            - (50%) normal

Who Falls Under the Category of Functional Heartburn?

- Patient with heartburn
- Endoscopy
- Normal endoscopy
- pH testing

- (50%) abnormal
- Positive (37%)
  - Symptom index
    - Negative (63%)
      - PPI treatment
    - NERD

Who Falls Under the Category of Functional Heartburn?

Patient with heartburn → Endoscopy → Normal endoscopy → pH testing → (50%) abnormal

Positive (37%) Responsive → Symptom index → Negative (63%) PPI treatment

(50%) normal

NERD

Who Falls Under the Category of Functional Heartburn?

- Patient with heartburn
  - Endoscopy
    - Normal endoscopy
      - pH testing
        - (50%) abnormal
          - Positive (37%)
            - Responsive
              - NERD
              - Functional heartburn
        - (50%) normal
          - Symptom index
            - Negative (63%)
              - Not responsive
              - PPI treatment

NERD, Functional Reflux Hypersensitivity and Functional Heartburn – The Future!

Patient with heartburn

Endoscopy

Normal endoscopy

pH testing

Normal 50%

50% abnormal

37% Positive

Responsive

NERD

Functional reflux hypersensitivity

Symptom index

Negative 63%

Not responsive

PPI treatment

Responsive

Functional heartburn
Clinical Characteristics of Patients with Functional Heartburn

- Females
- Young / middle age
- Other functional bowel disorders
  - NCCP
  - Functional dyspepsia
- Psychological comorbidity
  - Somatization
  - Depression/Anxiety

## Functional Heartburn Characteristics

<table>
<thead>
<tr>
<th></th>
<th>FH (Rome II)</th>
<th>NERD (pH-positive)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F &gt; M</td>
<td>F &gt; M</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age</td>
<td>46</td>
<td>43</td>
<td>NS</td>
</tr>
<tr>
<td>H pylori positive</td>
<td>30–45%</td>
<td>30–50%</td>
<td>NS</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>20%</td>
<td>20%</td>
<td>NS</td>
</tr>
<tr>
<td>Hx/O heartburn (yrs)</td>
<td>7.5</td>
<td>3.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Chest pain episodes</td>
<td>Once a week</td>
<td>Once a month</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>Similar</td>
<td>Similar</td>
<td>NS</td>
</tr>
<tr>
<td>Symptom frequency</td>
<td>Similar</td>
<td>Similar</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant FBD</td>
<td>Similar</td>
<td>Similar</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant other GI disorders</td>
<td>Similar</td>
<td>Similar</td>
<td>NS</td>
</tr>
<tr>
<td>HRQOL (SF-30)</td>
<td>Similar</td>
<td>Similar</td>
<td>NS</td>
</tr>
</tbody>
</table>

Comparative Assessment of the Psychological Profile of NERD versus FH Patients Using the SCL-90R

Functional Dyspepsia is Very Common in Functional Heartburn Patients


* * *
A Functional Heartburn Patient
## Functional Heartburn Using Impedance + pH

<table>
<thead>
<tr>
<th></th>
<th>Acid</th>
<th>Weakly acid</th>
<th>Liquid</th>
<th>Mixed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upright</td>
<td>7</td>
<td>11</td>
<td>1</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Supine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>11</td>
<td>1</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>

**pH** - Upright 0.9%, Supine 0 Total 0.5%

**SI/SAP** – Both Negative for heartburn
Heartburn!

- Esophageal symptoms are not stimulus specific (No acid ≠ No heartburn)
Esophageal symptoms are not stimulus specific (No acid ≠ No heartburn)

The esophagus has a very limited repertoire of symptoms
Heartburn!

- Esophageal symptoms are not stimulus specific (No acid ≠ No heartburn)
- The esophagus has a very limited repertoire of symptoms
- Heartburn can result from different intra-esophageal events
Heartburn!

- Esophageal symptoms are not stimulus specific (No acid ≠ No heartburn)
- The esophagus has a very limited repertoire of symptoms
- Heartburn can result from different intra-esophageal events
- Functional heartburn is real
Heartburn, Not Chest Pain, is the Most Common Symptom in Response to Esophageal Distension in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Total number of distensions</th>
<th>Number of HB</th>
<th>Number of CP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constant volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before atropine (11 subjects)</td>
<td>297</td>
<td>73 (24.6%)</td>
<td>19 (6.5%)</td>
</tr>
<tr>
<td>After atropine (11 subjects)</td>
<td>277</td>
<td>62 (22.4%)</td>
<td>21 (7.6%)</td>
</tr>
<tr>
<td><strong>Constant pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before atropine (7 subjects)</td>
<td>108</td>
<td>15 (13.9%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>After atropine (6 subjects)</td>
<td>90</td>
<td>17 (18.9%)</td>
<td>4 (4.4%)</td>
</tr>
</tbody>
</table>
Putative Mechanisms of Heartburn in Patients with Functional Heartburn

- Esophageal hypersensitivity
- Abnormal central processing of esophageal signals
- Hypervigilance
- Emotionally-related factors
- Psychological comorbidity

Esophageal Hypersensitivity

The perception of non-painful esophageal stimuli as being painful and the perception of painful esophageal stimuli as being more painful.
Patients with Functional Heartburn Are More Likely to Report Retrosternal Discomfort During Wireless pH Monitoring
Functional Heartburn and Esophageal Hypersensitivity

Functional Heartburn and Esophageal Hypersensitivity

75% of FH
Esophageal Hypersensitivity in Subtypes of Gastroesophageal Reflux Disease

The Relationship Between Histopathological Analysis and GERD Phenotype

Histopathology of Functional Heartburn Using Dilated Intercellular Spaces

Implications of Functional Heartburn

- Psychological comorbidity
- Compliance
  - Improper dosing time
- Eosinophilic esophagitis (?)
- Weakly acidic reflux
- Duodenogastroesophageal reflux
- Residual acid reflux
- Delayed gastric emptying
- Concomitant functional bowel disorder

- Reduced PPI bioavailability
- Rapid PPI metabolism
- PPI resistance
- Others

Implications of Functional Heartburn

- Psychological comorbidity
- Compliance
- Improper dosing time
- Eosinophilic esophagitis (?)
- Weakly acidic reflux
- Duodenogastroesophageal reflux
- Residual acid reflux
- Delayed gastric emptying
- Concomitant functional bowel disorder

- Reduced PPI bioavailability
- Rapid PPI metabolism
- PPI resistance
- Others

How Common is Functional Heartburn in Patients with Heartburn Who Failed PPI BID?

Symptomatic patients
172 (86%)

Nonacid reflux
61 (35%)

Acid reflux
13 (8%)

Symptoms not associated with reflux
98 (57%) = Func. HB

Treatment of Functional Heartburn

• Very limited data
Treatment of Functional Heartburn

- Very limited data
- Treat with pain modulators
Treatment of Functional Heartburn

- Very limited data
- Treat with pain modulators
- Address psychological comorbidity if present
Treatment of Functional Heartburn

• Very limited data
• Treat with pain modulators
• Address psychological comorbidity if present
• Do not shy away from comprehensive approach as well as alternative/complimentary medicine
Functional Heartburn: Pain Modulators

- **Antidepressants**
  - TCAs, SSRIs, SNRIs and trazodone

- **Adenosin agonists** (theophylline)

- **Serotonin agonists** (tegaserod)

- **Antiepileptics** (pregabalin)

- **Peripheral neuropathy analgesics** (gabapentin)

- In partial responders – combine with a PPI

## Pain Modulators for the Treatment of Functional Esophageal Disorders

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Dose</th>
<th>Disorder</th>
<th>RCT</th>
<th>Side effects</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine$^{25}$</td>
<td>50 mg/d</td>
<td>NCCP</td>
<td>+</td>
<td>+/-</td>
<td>57%</td>
</tr>
<tr>
<td>Amitriptyline$^{29,30}$</td>
<td>10-20 mg/day</td>
<td>NCCP, globus</td>
<td>+</td>
<td>+/-</td>
<td>52%</td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline$^{31}$</td>
<td>50-200 mg/day</td>
<td>NCCP</td>
<td>+</td>
<td>+</td>
<td>57%</td>
</tr>
<tr>
<td>Paroxetine$^{32}$</td>
<td>50-75 mg/day</td>
<td>NCCP</td>
<td>+</td>
<td>+/-</td>
<td>Modest</td>
</tr>
<tr>
<td>Citalopram$^{31}$</td>
<td>20 mg/day</td>
<td>ES</td>
<td>+</td>
<td>+/-</td>
<td>Significant</td>
</tr>
<tr>
<td>Paroxetine$^{33}$</td>
<td></td>
<td>NCCP</td>
<td>+</td>
<td>++</td>
<td>None</td>
</tr>
<tr>
<td>Trazodone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone vs clomipramine$^{28}$</td>
<td>50 mg/25 mg/day</td>
<td>NCCP</td>
<td>-</td>
<td>+</td>
<td>Modest</td>
</tr>
<tr>
<td>Trazodone$^{34}$</td>
<td>100-150 mg/day</td>
<td>Dysmotility</td>
<td>+</td>
<td>+/-</td>
<td>41.29%</td>
</tr>
<tr>
<td>SNRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine$^{35}$</td>
<td>75 mg/day</td>
<td>NCCP</td>
<td>+</td>
<td>++</td>
<td>52%</td>
</tr>
<tr>
<td>Other pain modulators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline$^{40,41}$</td>
<td>200 mg x2/day</td>
<td>NCCP</td>
<td>+</td>
<td>+/-</td>
<td>58%</td>
</tr>
<tr>
<td>Gabapentin$^{47}$</td>
<td>300 mg x3/day</td>
<td>Globus</td>
<td>+</td>
<td>+/-</td>
<td>66%</td>
</tr>
</tbody>
</table>

TCAs, tricyclic antidepressants; NCCP, non-cardiac chest pain; RCT, randomized control trial; ES, esophageal hypersensitivity; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors.
Receptor Activity and Dosages for TCA Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor activity</th>
<th>Dosage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NE</td>
<td>5-HT</td>
<td>H₁</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>+2</td>
<td>+2</td>
<td>+4</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+2</td>
<td>+2</td>
<td>+4</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+4</td>
<td>+2</td>
<td>+1</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+3</td>
<td>+2</td>
<td>+2</td>
</tr>
</tbody>
</table>

NE, norepinephrine; 5-HT, 5-hydroxytryptamine; H₁, histamine-H₁ receptor, Ach, acetylcholine.
How to Use TCAs in Practice

**Main Principle: “Low and slow”**

- Start 10 mg at bedtime
- Increase by 10 mg increments weekly
- Goal of treatment 30 mg–50 mg once daily
- If side effects emerge:
  - Decrease to a lower dose
  - Can switch to another TCA
- May combine with SSRIs

TCAs - Low Dose

• Dosing: 5 – 10mg at bed time for 3-4 weeks before increasing the dose

• Explain to patients that response may take time
Tricyclic Antidepressants
Receptor Affinity Predicts Side Effects

Receptor Affinities*

\[ \checkmark \checkmark \checkmark - \checkmark \checkmark \]

\[ \checkmark - \checkmark \checkmark \]

* For acetylcholine, histamine, and adrenergic receptors
Receptor Activity and Dosages for SSRI and SNRI Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor activity</th>
<th>Dosage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NE</td>
<td>5-HT</td>
<td>ACh</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-</td>
<td>+4</td>
<td>-</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>-</td>
<td>+4</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>-</td>
<td>+4</td>
<td>+1</td>
</tr>
<tr>
<td>Sertraline</td>
<td>-</td>
<td>+4</td>
<td>-</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+4</td>
<td>+3</td>
<td>-</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>+4</td>
<td>+4</td>
<td>-</td>
</tr>
</tbody>
</table>

NE, norepinephrine; 5-HT, 5-hydroxytryptamine; H₁, histamine-H₁ receptor, Ach, acetylcholine.
The Effect of Citalopram 20mg Once Daily vs. Placebo on Patients with the Hypersensitive Esophagus

- A randomized, double-blind, placebo-controlled trial for 6 months
- % of patients who continued to report symptoms after full course of treatment

Comparing Omeprazole with Fluoxetine for Treatment of Patients with Heartburn and Normal Endoscopy who Failed Once Daily Proton Pump Inhibitors: Double-Blind Placebo-Controlled Trial

<table>
<thead>
<tr>
<th>Pain Reduction</th>
<th>Global Health Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Venlafaxine</td>
<td>1. Venlafaxine</td>
</tr>
<tr>
<td>2. Sertraline</td>
<td>2. Sertraline</td>
</tr>
<tr>
<td>3. Imipramine</td>
<td>3. Trazodone</td>
</tr>
<tr>
<td>4. Trazodone</td>
<td>4. Imipramine</td>
</tr>
<tr>
<td>5. Paroxetine</td>
<td>5. Paroxetine</td>
</tr>
</tbody>
</table>
Efficacy of Venlafaxine (75 mg qhs) vs. Placebo on the Mean Intensity Symptom Score

Antidepressants With the Best Evidence to Support Their Use in a Functional Esophageal Disorder

<table>
<thead>
<tr>
<th>Esophageal Disorder</th>
<th>Medication</th>
<th>Class</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional chest pain</td>
<td>Imipramine</td>
<td>TCA</td>
<td>25-50mg</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>SSRI</td>
<td>50-200mg</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>SNRI</td>
<td>75mg</td>
</tr>
<tr>
<td>Hypersensitive Esophagus</td>
<td>Citalopram</td>
<td>SSRI</td>
<td>20mg</td>
</tr>
<tr>
<td>Refractory GERD</td>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>20mg</td>
</tr>
<tr>
<td>Globus</td>
<td>Amitriptyline</td>
<td>TCA</td>
<td>25mg</td>
</tr>
</tbody>
</table>

## Esophageal Pain Modulators

- **Adenosin agonists** (theophylline)
- **5-HT4 agonists** (tegaserod)
- **5-HT3 antagonists** (octreotide)
- **Antiepileptics** (pregabalin)
- **Peripheral neuropathy analgesics** (gabapentin)
- **Somatostatin analog** (octreotide)
The Role of Acupuncture in Refractory GERD

Address Psychological Co-Morbidity in Functional Heartburn
Address Psychological Co-Morbidity in Functional Heartburn

*Anxiety
Address Psychological Co-Morbidity in Functional Heartburn

*Anxiety
*Depression
Address Psychological Co-Morbidity in Functional Heartburn

*Anxiety
*Depression
*Somatization
Address Psychological Co-Morbidity in Functional Heartburn

*Anxiety
*Depression
*Somatization

I took my Prozac today