Approach to Patients with Non-Cardiac Chest Pain

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NONCARDIAC CHEST PAIN
A GROWING MEDICAL PROBLEM

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Definition

Noncardiac chest pain is defined as recurrent chest pain that is indistinguishable from ischemic heart pain after a reasonable work-up excluded a cardiac cause.

Community-based Prevalence Rates of Noncardiac Chest Pain Around the World

Population Prevalence Rates of Noncardiac Chest Pain by Age and Gender

Impact of Non-Cardiac Chest Pain on Health Care Utilization

- See a physician for chest pain: 75%
- Unemployed: 50%
- Poor quality of life: 50%
- On cardiac meds: 50%
- Reassured: 30%

Common Noncardiac, Nonesophageal Etiologies for Chest Pain

1. **Musculoskeletal**
   a. Tietze’s syndrome
   b. Costochondritis
   c. Fibromyalgia
   d. Precordial catch syndrome
   e. Slipping rib syndrome

2. **Gastrointestinal**
   a. Gastric
   b. Biliary tree
   c. Pancreatic
   d. Intra-abdominal masses (benign and malignant)

3. **Pulmonary**
   a. Pneumonia
   b. Pulmonary embolus
   c. Lung cancer
   d. Pneumothorax and pneumomediastinum
   e. Pleural effusions
   f. Intrathoracic masses (benign and malignant)

3. **Miscellaneous**
   a. Aortic disorders
   b. Pericarditis and myositis
   c. Pulmonary hypertension
   d. Herpes zoster
   e. Drug-induced pain
   f. Sickle cell crisis
   g. Psychological disorders

Achem and DeVault, in Fass and Eslick, *NCCP–A Growing Medical Problem 2007*
Frequency of diagnoses in patients admitted with acute chest pain who have not had myocardial infarction

Esophageal and Nonesophageal Causes of NCCP

- Miscellaneous
- Musculoskeletal disorders
- Panic disorder
- Pulmonary/pericardial disorders
- Gastric/biliary/pancreatic disorders
- Psychological comorbidity
- Esophageal disorders
  - Esophageal dysmotility 15%–18%
  - Gastroesophageal reflux disease 50%–60%
  - Chest pain of presumed esophageal origin 32%–35%

Prevalence of GERD and GERD-Related Abnormalities in Patients Presenting with NCCP

Prevalence of GERD
- 25%
- 60%

Prevalence of abnormal acid exposure
- 50%
- 60%

Prevalence of erosive esophagitis
- 10%
- 70%

The Limited Repertoire of Pain-Related Symptoms of the Esophagus

Chest Pain and Esophageal Dysmotility – The Clinical Outcomes Research Initiative (CORI) Experience

66 University, VA and Non-Academic Centers

N = 160

- Hypotensive LES: 18%
- Hypertensive LES: 3%
- Nutcracker Esophagus: 3%
- NSEMD: 3%
- Ineffective Peristalsis: 2%
- Achalasia: 0.5%
- DES: 0.5%

Distal Esophageal Spasm
Hypercontractile Esophagus
(Jackhammer)
Case 9 - A 56 Y/o woman with history of episodic chest pain, without dysphagia, that occur almost daily
Chest Pain of Presumed Esophageal Origin – Functional Chest Pain

Rome III Diagnostic Criteria

Must include all of the following:

1. Midline chest pain or discomfort that is not of burning quality
2. Absence of evidence that gastroesophageal reflux is the cause of the symptom
3. Absence of histopathology-based esophageal motility disorders

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
The Irritable Esophagus

A Frequent Cause of Angina-Like Pain

“These observations strongly suggest that there is a group of patients in whom irritability of the esophagus plays an important part in the production of angina-like chest pain.”

Esophageal Hypersensitivity

The perception of non-painful esophageal stimuli as being painful and painful esophageal stimuli as being more painful.

Acid Reflux into the Distal Esophagus Results in Somatic and Visceral Stimulation in NCCP Patients

Upper esophagus hypersensitivity (secondary Hyperalgesia)

Lower esophagus hypersensitivity (Primary Hyperalgesia)

Chest wall hypersensitivity

Evaluation

Cardiac/noncardiac

i. Patients presenting with chest pain should initially undergo an evaluation by a cardiologist to exclude a cardiac cause.

ii. Patients with NCCP should be evaluated first for GERD as the underlying cause for their symptoms.

Fass and Achem. *Dis Esophagus* 2011
Assessment for GERD - The PPI Test

“The use of a short course of high dose PPI as a test in diagnosing GERD”

## PPI Therapeutic Trials in NCCP

<table>
<thead>
<tr>
<th>Author</th>
<th>Dosing Schedule</th>
<th>Number of Patients</th>
<th>Patients with 50% symptom improvement (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xie et al.</td>
<td>Lansoprazole: 30 mg day⁻¹ x 4 weeks</td>
<td>68</td>
<td>53</td>
<td>92</td>
<td>67</td>
</tr>
<tr>
<td>Pandak et al.</td>
<td>Omeprazole: 40 mg twice daily X 2 weeks</td>
<td>37</td>
<td>71</td>
<td>90</td>
<td>67</td>
</tr>
<tr>
<td>Fass et al.</td>
<td>Omeprazole: 40 mg in the AM and 20mg in PM x 7 days</td>
<td>37</td>
<td>78</td>
<td>78</td>
<td>87</td>
</tr>
<tr>
<td>Bautista et al.</td>
<td>Lansoprazole: 60 mg in the AM and 30 mg n the PM x 7 days</td>
<td>40</td>
<td>78</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Dickman et al.</td>
<td>Rabeprazole: 20 mg in the AM and 20 mg in the PM x 7 days</td>
<td>20</td>
<td>75</td>
<td>83</td>
<td>75</td>
</tr>
</tbody>
</table>

**Evaluation, cont’d**

**pH testing**

i. Ambulatory 24-hour esophageal pH monitoring should be reserved for NCCP patients in whom objective evidence of GERD is required (off therapy) or in whom response to a therapeutic PPI trial is equivocal or negative (on therapy).

ii. Extending pH monitoring (48 hours) using the wireless pH capsule, improves detection of reflux-associated chest pain symptoms.

Value of Extended Recording Time with Wireless pH Monitoring in Evaluating GERD

## Upper Endoscopy in NCCP Patients
*(A Large Multicenter Consortium)*

<table>
<thead>
<tr>
<th>Findings</th>
<th>Chest Pain Group N = 3688 (%)</th>
<th>Reflux Group N = 32,981 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’s esophagus</td>
<td>163 (4.4%)</td>
<td>3016 (9.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Esophageal inflammation</td>
<td>715 (19.4%)</td>
<td>9153 (27.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>1053 (28.6%)</td>
<td>14,775 (44.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normal</td>
<td>1627 (44.1%)</td>
<td>12,801 (38.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stricture/Stenosis</td>
<td>132 (3.6%)</td>
<td>1223 (3.7%)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Provocative Testing in NCCP

- Bethanechol test
- Pentagastrin test
- Edrophonium (Tensilon) test (0 - 50%)
- Ergonovine test
- Acid perfusion test (10 - 38%)
- Balloon distension test (5 - 40%)

In Fass et al, Therapy in Digestive Disorders, 2nd Ed, 2006
Psychological comorbidity, such as depression, panic disorder, and anxiety, is common in NCCP patients.
Treatment of NCCP
**GERD-Related NCCP**

**Omeprazole 20mg BID for 8 weeks**

Therapeutic Modalities of non-GERD-Related NCCP

- Muscle relaxants (nitrates, Ca channel blockers)
- Botulinum toxin
- Pain modulators (trazodone, TCAs, SSRIs, theophylline)
- Surgery for motility disorders
- Cognitive-behavioral therapy / hypnotherapy

Schmulson & Valdivinos, Gastroenterol Clin N Am 33:93-105, 2004
Chest Pain in Patients With Nutcracker Esophagus

Oral Nifedipine 10-30mg TID versus Placebo (14 weeks)

Botulinum Toxin for NCCP Patients with Spastic Esophageal Motility Disorder

29 patients with non-achalasia, non-GERD related, spastic esophageal motility disorders

What is the Current Treatment for Functional Chest Pain

- Tricyclic antidepressants
- Trazadone
- Selective serotonin reuptake inhibitors
- Adenosine antagonists
- Cognitive behavioral therapy
- Hypnotherapy
- Alternative therapy (Johrei therapy etc.)

Hershcovici et al. Aliment Pharmacol Ther 2012;35::5-14
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</td>
<td>50 mg/d</td>
<td>NCCP</td>
<td>+</td>
<td>+/-</td>
<td>57%</td>
</tr>
<tr>
<td>Amitriptyline</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</td>
<td>50-200 mg/day</td>
<td>NCCP</td>
<td>+</td>
<td></td>
<td>57%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>50-75 mg/day</td>
<td>NCCP</td>
<td>+</td>
<td>+/-</td>
<td>Modest</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20 mg/day</td>
<td>ES</td>
<td>+</td>
<td>+/-</td>
<td>Significant</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg/day</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</td>
<td>50 mg/25 mg/day</td>
<td>NCCP</td>
<td>-</td>
<td>+</td>
<td>Modest</td>
</tr>
<tr>
<td>Trazodone</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</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</td>
<td>200 mg ×2/day</td>
<td>NCCP</td>
<td>+</td>
<td>+/-</td>
<td>58%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg ×3/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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NE</td>
<td>5-HT</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>+2</td>
<td>+2</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+2</td>
<td>+2</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+4</td>
<td>+2</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+3</td>
<td>+2</td>
</tr>
</tbody>
</table>

NE, norepinephrine; 5-HT, 5-hydroxytryptamine; H<sub>1</sub>, histamine-H<sub>1</sub> 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

TCA’s - Low Dose

- Dosing: 5 – 10mg at bed time for 3-4 weeks before increasing the dose.
- Explain patients that response may take time
Tricyclic Antidepressants
Receptor Affinity Predicts Side Effects

Amitriptyline
Imipramine
Doxepin

Nortriptyline
Desipramine

* For acetylcholine, histamine, and α-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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NE</td>
<td>5-HT</td>
<td>ACh</td>
<td>Initial</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-</td>
<td>+4</td>
<td>-</td>
<td>10-20</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>-</td>
<td>+4</td>
<td>-</td>
<td>25-50</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>-</td>
<td>+4</td>
<td>+1</td>
<td>10-20</td>
</tr>
<tr>
<td>Sertraline</td>
<td>-</td>
<td>+4</td>
<td>-</td>
<td>25-50</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+4</td>
<td>+3</td>
<td>-</td>
<td>25-50</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>+4</td>
<td>+4</td>
<td>-</td>
<td>20-40</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

% of Patients

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>N=39</th>
<th>N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram 20mg once daily</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P=0.02

Viazis Am J Gastro 2012
Efficacy of Venlafaxine (75 mg qhs) or Placebo on the Mean Intensity Symptom Score

## Hierarchy of Antidepressants for Esophageal Pain Reduction and Global Health Improvement

<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>

The Effect of Oral Theophylline on the Number of Painful Days in Each Subject


N = 24
Percentage of Patients Reporting a Global Improvement in Chest Pain or General Well-being with Either Hypnotherapy (n=15) or Supportive Therapy (n=13)

Jones et al, Gut 2006;55:1403-1408
The Effect of Johrei vs. Wait List on Symptoms of Patients with Chest Pain of Presumed Esophageal Origin—A Randomized Trial

[Diagram showing comparison between Johrei (N=16) and Wait list (N=14) groups for symptom intensity at baseline and treatment over 6 weeks. The bar chart indicates a significant difference (P=0.0032) after 6 weeks of treatment.]

Navarro-Rodriguez T, submitted to DDW 2008
NCCP patients referred to a gastroenterologist

Alarm symptoms

PPI test or PPI empirical trial

- Taper down to the lowest PPI dose that controls patient symptoms

- Maintenance treatment

+ Esophageal manometry

- Achalasia
  • Medical
  • Endoscopic
  • Surgical

- Spastic motility disorder
  • Pain modulators
  • Cognitive therapy
  • Hypnotherapy

+ Upper endoscopy

- Treat mucosal abnormality