Figure 2: Recurrent chest pain of suspected esophageal origin

1. Patient with chest pain of suspected esophageal origin

2. History and physical exam. suggestive of non-esophageal etiology?
   - yes: Evaluate and treat as indicated
   - no: Proceed to step 4

4. Risk of cardiac etiology?
   - yes: Cardiological evaluation
   - no: Proceed to step 8

5. Cardiological evaluation
   - yes: Identify any abnormality?
     - yes: Reflux disease with chest pain: titrate PPI therapy
     - no: Proceed to step 9
   - no: Proceed to step 6

6. Any abnormality identified?
   - yes: Ischemic heart disease, pericarditis
   - no: Proceed to step 10

8. Trial of twice daily proton pump inhibitor (PPI)
   - yes: Chest pain resolved?
     - yes: Reflux disease with chest pain: titrate PPI therapy
     - no: Proceed to step 9
   - no: Proceed to step 11

9. Chest pain resolved?
   - yes: Reflux disease with chest pain: titrate PPI therapy
   - no: Proceed to step 10

10. Any abnormality identified?
    - yes: Reflux disease with chest pain: titrate PPI therapy
    - no: Proceed to step 18

11. Upper GI endoscopy ± biopsy

12. Any abnormality identified?
    - yes: LA A-D esophagitis, pill esophagitis, infectious esophagitis
      - yes: LA A-D esophagitis
      - no: Proceed to step 16
    - no: Proceed to step 13

13. LA A-D esophagitis, pill esophagitis, infectious esophagitis
   - yes: Non-erosive reflux disease
   - no: Proceed to step 15

14. PH or impedance-PH monitoring (off of PPIs)
    - yes: Abnormal esophageal acid exposure?
      - yes: Non-erosive reflux disease
      - no: Proceed to step 18
    - no: Proceed to step 18

15. Abnormal esophageal acid exposure?
    - yes: Positive symptom association probability?
      - yes: Achalasia, diffuse esophageal spasm
      - no: Non-erosive reflux disease
    - no: Non-erosive reflux disease

16. Positive symptom association probability?
    - yes: Achalasia, diffuse esophageal spasm
    - no: Non-erosive reflux disease

17. Esophageal manometry
    - yes: Achalasia, diffuse esophageal spasm
    - no: Non-erosive reflux disease

18. Esophageal manometry
    - yes: Achalasia, diffuse esophageal spasm
    - no: Non-erosive reflux disease

19. Meets esophageal motor disorder criteria?
    - yes: Achalasia, diffuse esophageal spasm
    - no: Non-erosive reflux disease
Recurrent chest pain of suspected esophageal origin

Case history

A 72-year old retired school teacher consults a gastroenterologist upon referral by her cardiologist. In the past two years she has experienced numerous episodes of severe retrosternal pain radiating to the jaw and left arm; at times there is also radiation of the pain to the midline of the back (Box 1, Fig 2). Prior to the onset of the chest pain the patient has rarely had health problems. Her appendix was removed at age 22 years and she underwent hysterectomy at age 52 years because of fibroid tumors. She has no relevant family history of gastrointestinal disease.

The chest pain occurs at an average rate of two episodes per week, but there are large variations in its rate of occurrence; it is described as a heavy sensation. The onset of the pain is not clearly related to meal intake and there is no dysphagia, either during chest pain episodes, or in between. There is no typical heartburn, regurgitation or odynophagia. The onset of the pain is not clearly related to exercise or body posture and physical examination of the lungs and chest wall is normal (Box 2). On three occasions she has been admitted to the coronary care unit of a large general hospital. In all cases no evidence of myocardial ischemia or infarction was found. Chest X-Ray had been normal. Coronary angiography had revealed normal coronary arteries, and exercise testing was negative (Boxes 5 and 6). Prior to referral to the gastroenterologist a therapeutic trial of omeprazole 40mg twice daily had been given (Box 8). After 6 weeks of this treatment the patient reported that the chest pain had continued to occur (Box 9).

The gastroenterologist performs an upper GI endoscopy (Box 11), during which a normal squamocolumnar junction is seen, positioned 1 cm proximal to the diaphragmatic impression (Box 12). At this stage the gastroenterologist decides to arrange some additional tests. Esophageal manometry (Box 18) followed by 24-hour esophageal pH monitoring off a proton pump inhibitor (Box 14) shows normal peristalsis, normal LES function (Box 19) and physiological acid exposure (time with pH <4 3.2 %) (Box 15). During the 24-study no
chest pain episodes occurred, and therefore a positive symptom association probability could not be established (Box 17). A diagnosis of *functional chest pain of presumed esophageal origin* is made (Box 21).
**Figure Legend**

1. Esophageal chest pain is typically described as retrosternal with radiation to the midline of the back. It can be a heavy sensation and closely mimic cardiac pain. Radiation to the jaws and to the left arm may also occur.

2. History and physical should seek evidence of musculoskeletal, pulmonary, or neurological etiologies of chest pain.

3. If an alternative diagnosis that is typically associated with chest pain is established this would conclude the evaluation for functional esophageal chest pain.

4. It is important to adequately consider the risk of potentially fatal cardiac conditions prior to pursuing an esophageal evaluation. This need not always mean cardiological referral but if doubt exists, it is best to err on the side of caution.

5. Relevant cardiological evaluation may include exercise stress testing, Holter monitoring and coronary angiography depending on symptom features and risk factors (27).

6. If a cardiological diagnosis that is typically associated with chest pain is established this would conclude the evaluation for functional esophageal chest pain.

7. Although other cardiological diagnoses could potentially explain chest pain, the two with most immediate consequence are coronary artery disease and pericarditis.

8. For the indication of suspected reflux related chest pain, a 4 week trial of twice daily PPI is indicated (28).

9. If PPI therapy is associated with a satisfactory improvement or resolution of chest pain this would conclude the evaluation for functional esophageal chest pain.
10. Once a satisfactory response has been achieved, the PPI dosage should be reduced to the least amount that is still associated with a satisfactory treatment effect.

11. Biopsies should be obtained at the time of endoscopy if there are any visual abnormalities suggestive of metaplasia, ulceration, infection, eosinophilic esophagitis, or if dysphagia was an additional presenting symptom.

12. Endoscopic findings diagnostic of a painful esophageal condition would conclude the evaluation for functional esophageal chest pain.

13. The most common cause of esophageal chest pain is gastro-esophageal reflux disease (3) but other causes of esophageal ulceration such as caustic, infectious, or pill-induced esophagitis may be encountered. The Los Angeles Classification of esophagitis is based on the occurrence and extent of visible mucosal breaks in the distal esophageal mucosa. Los Angeles A is the mildest with only short breaks (<5mm) confined to folds of the epithelium while Los Angeles D is the most severe with nearly circumferential breaks (15).

14. pH or impedance-pH monitoring is performed after withholding PPI therapy for 7 days to obtain a meaningful assessment of esophageal acid exposure and to provide the greatest chance of finding a positive association between heartburn episodes and reflux events.

15. The cutoff for abnormal esophageal acid exposure is typically <5%, although this value varies slightly among centers (19).

16. Abnormal esophageal acid exposure or a positive symptom association probability are diagnostic of non-erosive reflux disease by Rome III criteria. This would then establish a diagnosis of a reflux chest pain syndrome (and exclude functional chest pain).

17. The Symptom Association Probability (SAP) is a statistical test to determine if the co-occurrence of symptoms and reflux events within 2-minute periods is happening by chance or because the two are likely
related (22). An SAP >95% equates to a p<0.05 that they are related. Although some centers use the Symptom Index (SI) to gauge symptom-reflux association, the SI is not a validated method and has no statistical basis (23).

18. If reflux cannot be identified as the cause of the chest pain, esophageal manometry is indicated. It is preferable to obtain a high-resolution manometry (esophageal pressure topography) study if available because of a greater sensitivity in the diagnosis of achalasia. (24).

19. For the purposes of establishing a diagnosis of functional chest pain the only two exclusionary diagnoses are achalasia or DES. According to the Rome III criteria, other, less severe peristaltic abnormalities are still consistent with a diagnosis of functional chest pain.

20. Achalasia is defined by absent peristalsis and impaired deglutitive LES relaxation; DES by ≥20% of test swallows exhibiting simultaneous or spastic contractions in the distal esophagus (25).

21. Rome III diagnostic criteria for functional chest pain of presumed esophageal origin are: 1) midline chest pain that is not of burning quality, and 2) absence of evidence that gastroesophageal reflux is the cause of the symptom, and 3) absence of histopathology-based esophageal motility disorders, and 4) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (26-29).