A SYSTEMATIC APPROACH TO MEDICALLY UNEXPLAINED SYMPTOMS

Chronic Non-Cardiac Chest Pain & Palpitations

Jeffrey B. Geske, MD
Professor of Medicine

August 17-20, 2022
The Ritz-Carlton, Half Moon Bay

@MayoClinicGIM
@jeffreygeske
Disclosure

Relevant Financial Relationships
None

Off-Label/Investigational Uses
None
Acknowledgement

Michael W. Cullen, MD
Chronic chest pain and palpitations

- Angina
- Pleurisy
- COPD
- Congestive heart failure
- Atrial fibrillation
- Atrial flutter
- Costochondritis
- Anxiety
- Obstructive sleep apnea
- Supraventricular tachycardia
- Cardiomyopathies
- Ventricular tachycardia
- Gastroesophageal reflux
- Pericarditis
- Depression
- Coronary vasospasm
- Coronary vasospasm
- Coronary vasospasm
- Coronary vasospasm
Learning objectives

1. Differentiate important clinical diagnoses that might be dismissed as medically unexplained chest pain or palpitations.

2. Review the evaluation and management of patients with specific conditions that frequently present as chronic chest pain or palpitations.

3. Manage patients with otherwise undiagnosed chronic chest pain or palpitations.
Case #1
59-year-old female

• 4-6 months of progressive “tightening” in chest radiating to jaw
• Worse with stress or physical activity
• Better with rest
• Associated with exertional dyspnea
• Cardiac risk factors
  • Diabetes mellitus
  • Hypertension
  • Prior smoking
  • Hyperlipidemia
59-year-old female
Exertional chest tightness

- Atenolol 100 mg daily
## Assessment of chest pain

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤39</td>
<td>Male</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Intermediate</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>40-49</td>
<td>Male</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>50-59</td>
<td>Male</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>≥60</td>
<td>Male</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

**Category**

- **High** ≥90%
- **Intermediate** 10-90%
- **Low** 5-10%
- **Very low** ≤5%
Exercise echocardiogram

- Remained in Stage 1 of Bruce protocol
- Chest pain with exercise
- Peak heart rate → 111 bpm (69% predicted)
- Peak double product → 19,092 bpm x mmHg
- No ischemic ECG changes
Exercise echocardiogram
Exercise echocardiogram

- Negative for ischemia at the workload achieved
- Limited exercise capacity
- Ejection fraction 65% → 70%
- No stress-induced regional wall motion abnormalities
What is your next step?

A. Observation
B. Exercise sestamibi test
C. Regadenoson sestamibi test
D. Dobutamine stress echo
E. CT coronary angiogram
F. Invasive coronary angiogram
Dobutamine echocardiogram

- Dobutamine: 5 → 40 mcg/kg/min
- Atropine 2 mg
- Peak heart rate → 125 bpm (78% age-predicted maximum)
- No ECG changes
Dobutamine echocardiogram

Rest

Low dose

LV

RV

Pre-peak

Peak

@MayoClinicGIM
Dobutamine echocardiogram

- Negative for ischemia
- Ejection fraction 65% → 75%
- No stress-induced regional wall motion abnormalities
What is your next step?

A. Observation
B. Regadenoson sestamibi test
C. Dobutamine stress MRI
D. CT coronary angiogram
E. Invasive coronary angiogram
Patient had symptoms very typical for angina...

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre-test probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥90%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10-90%</td>
</tr>
<tr>
<td>Low</td>
<td>5-10%</td>
</tr>
<tr>
<td>Very low</td>
<td>≤5%</td>
</tr>
</tbody>
</table>

Symptoms were progressing
Low workload on treadmill test
CT coronary angiogram

Focal stenosis in proximal RCA due to non-calcified plaque
Invasive coronary angiogram
Drug eluting stent to RCA
Why the negative stress echoes?

**Myocardial oxygen demand**
- Heart rate
- Afterload
- Wall tension
- Contractility

**Surrogates**
- Heart rate
- Blood pressure
- Double product

**Thresholds (arbitrary) for adequate stress**
- Heart rate ≥ 85% age predicted max
- Double product ≥ 20,000 bpm x mmHg

**Atenolol 100 mg daily**
- ↓ exercise capacity
- ↓ HR and BP response
- ↓ myocardial O$_2$ demand
- ↓ sensitivity of test

If the pre-test probability is high and the stress test results don’t fit, keep looking!
How can you keep looking?

CT coronary angiography

• Anatomic assessment of coronaries in patients with chest pain
• NOT same as a coronary calcium score!
  • Uses contrast
  • Requires ECG gating
  • Can be done with a coronary calcium score
• High negative predictive value
• Less accurate in calcified vessels
CT coronary angiography

What do the guidelines say?

CT coronary angiography is reasonable for the diagnosis of CAD in intermediate risk patients with...

- Symptoms despite prior normal testing
- Inconclusive results from prior testing
- Inability to undergo traditional stress testing

Class IIa
59-year-old female
Exertional chest tightening

Recognize symptoms of typical angina in patients with chronic chest pain

<table>
<thead>
<tr>
<th>Sub-sternal chest pain or discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked by exertion or emotional stress</td>
</tr>
<tr>
<td>Relieved by rest and / or nitroglycerin</td>
</tr>
</tbody>
</table>

If the stress test is negative and the pre-test probability is high, coronary CTA is an appropriate next step.
A quick word on other causes of chronic anginal pain…
Vasospastic angina
“Prinzmetal angina”
“Variant angina”

- Nitrate responsive angina
- Frequently nocturnal
- Ischemic ECG changes associated with pain
- Coronary artery spasm on provocative testing

Microvascular angina
“Cardiac syndrome X”
Coronary artery vasospasm

52-year-old man with 1 month of nightly chest pain, responsive to nitroglycerin

Baseline
Vasospastic angina
“Prinzmetal angina”
“Variant angina”

Nitrate responsive angina
Frequently nocturnal

Ischemic ECG changes associated with pain

Coronary artery spasm on provocative testing

Smoking cessation and lifestyle are critical!

CCB’s (i.e. diltiazem) are 1st line therapy

Microvascular angina
“Cardiac syndrome X”

Exertional angina
Ischemic stress tests

Normal epicardial coronaries

No epicardial coronary artery vasospasm with provocation

Abnormal coronary microvascular function

Sublingual nitroglycerin is 1st line therapy
Case #2
26-year-old female

- 1-2 years of palpitations
- <1-minute, multiple times per day
- Worse with stress or exercise
- Associated fleeting, sharp chest pain
- No pre-syncope or syncope
- No regular medications
- No other cardiac risk factors
26-year-old female
Palpitations and chest pain

• Normal vital signs
• Normal S1 and S2
• Mid-systolic click at apex
• 2/6 late systolic murmur at apex
• Prolongation of murmur with squat to stand
26-year-old female
Palpitations and chest pain

Holter monitor
- Sinus rhythm, average rate 65 bpm
- Rare atrial ectopic beats
- No ventricular ectopy or arrhythmias
26-year-old female
Palpitations and chest pain

Normal LV size, EF 65%
Myxomatous mitral valve leaflets
Bileaflet mitral valve prolapse
Mild mitral regurgitation
What is your next step?

A. Exercise stress echocardiogram
B. 30-day event monitor
C. Transesophageal echocardiogram
D. Electrophysiology referral for ICD implantation
E. Reassurance & repeat echocardiogram in 3 years
Mitral valve prolapse syndrome
Malignant mitral valve prolapse

Small portion of patients with MVP have ↑ risk of sudden cardiac death

- Pre-syncope or syncope
- T-wave inversion
- QTc prolongation
- Polymorphic PVCs or ventricular tachycardia

Diagram courtesy of Drs. John Giudicessi and Fatima Ezzeddine
Mitral valve prolapse syndrome

3488 patients Framingham Study

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Mitral valve prolapse (n=84)</th>
<th>No mitral valve prolapse (n=3407)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0 (0)</td>
<td>25 (0.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (1.2)</td>
<td>58 (1.7)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (1.2)</td>
<td>52 (1.5)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (3.6)</td>
<td>103 (3.0)</td>
</tr>
</tbody>
</table>

No difference in clinical findings

No difference in coronary disease or coronary risk factors

Patients with mitral valve prolapse more likely to have mitral regurgitation

Degree of mitral regurgitation associated with risk of arrhythmias
“Indeed, mitral valve prolapse is evolving into an interesting cause of mitral regurgitation rather than into a unique syndrome.”
## Monitoring mitral valve prolapse

### Frequency of echocardiograms in mitral regurgitation and normal left ventricular function

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Severity</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Mild</td>
<td>3-5 years</td>
</tr>
<tr>
<td>No</td>
<td>Moderate</td>
<td>1-2 years</td>
</tr>
<tr>
<td>No</td>
<td>Severe</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Yes</td>
<td>Severe</td>
<td>Operate!</td>
</tr>
</tbody>
</table>
What is your next step?

A. Exercise stress echocardiogram
B. 30-day event monitor
C. Transesophageal echocardiogram
D. Electrophysiology referral for ICD implantation
E. Reassurance & repeat echocardiogram in 3 years

Reassurance that palpitations are benign, chest pain non-cardiac. Monitor for mitral regurgitation

No risk factors for CAD
Benign Holter monitor, no risk factors for arrhythmias
Not additive to TTE in this case
No malignant features
26-year-old female
Palpitations and chest pain

Mitral valve prolapse is a primary valvular abnormality, not a clinical syndrome.

Evaluate chronic chest pain and palpitations in patients with mitral valve prolapse like you would any other patient.

Understand the intervals for surveillance echocardiography in patients with mitral regurgitation.
Case #3
42-year-old male

- 4 months of sharp chest discomfort
- Worse with deep breathing, laying supine
- Better sitting upright
- Otherwise, healthy, no cardiac risk factors
- Training for a marathon
  - No symptoms during exertion
  - Symptoms worse after exertion
42-year-old male
Sharp chest discomfort

Presented to ED 4 months ago:
- Diffuse, concave-up ST-elevation
- PR-segment depression

Diagnosed with acute pericarditis

Treated with NSAIDs x2 weeks

Symptoms initially improved

Returned after ~3 weeks, now less severe
42-year-old male
Sharp chest discomfort

• Vitals, physical exam normal
• ESR 22, CBC and electrolytes normal
• ECG
  • Sinus rhythm at 52 bpm
  • ST-segment changes resolved
• Echocardiogram
  • Ejection fraction 55%, valves normal
  • No effusion, no constrictive pericarditis
What is your next management step?

A. Exercise stress echocardiogram
B. Cardiac MRI
C. Oral prednisone x 3 months
D. Ibuprofen 800 mg tid, taper over 6 weeks
E. Ibuprofen 800 mg tid, taper over 6 weeks + colchicine 0.6 mg bid x 3 months
F. Reassurance
# Acute pericarditis

## Presentation

<table>
<thead>
<tr>
<th>History and physical</th>
<th>Sharp, positional chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>± Fever, recent infection</td>
</tr>
<tr>
<td></td>
<td>Pericardial friction rub</td>
</tr>
</tbody>
</table>

- Pericardial rub heard best at end-expiration
- Pleural rub heard best with respiration

**Most cases**
- Idiopathic
- Autoimmune
- Viral

**Other causes**
- Malignancy, uremia
- Trauma, radiation
- Meds (hydralazine)
Chronic pericarditis
Presentation

• Symptoms of acute pericarditis for >3 months
• Symptom-free period after acute treatment
• Ongoing symptoms usually less severe
• Common etiologies
  • Idiopathic, autoimmune, viral
  • Suboptimal treatment of acute pericarditis!
### Acute pericarditis

#### Treatment

**NSAID x 4-6 weeks**

- **Ibuprofen**
  - 800 mg tid x 2 weeks
  - Taper over next 4 weeks

- **Indomethacin**
  - 50 mg tid x 2 weeks
  - Taper over next 4 weeks

**Colchicine x 3 months**

- 0.6 mg bid (≥70 kg)
- 0.6 mg daily (<70 kg)
Acute pericarditis

Colchicine

240 patients with acute pericarditis

NSAID vs. NSAID + colchicine

NSAID + colchicine

NSAID alone

Colchicine

Absolute risk reduction = 21%

P<0.001

No. at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>NSAID alone</th>
<th>NSAID + colchicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>6</td>
<td>105</td>
<td>102</td>
</tr>
<tr>
<td>9</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>12</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>15</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>18</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

©2021 Mayo Foundation for Medical Education and Research | slide 51
Acute pericarditis

Treatment

Avoid glucocorticoids as first line therapy!

Early therapy with steroids increases recurrence risk!

NSAID x 4-6 weeks

**Ibuprofen**
- 800 mg tid x 2 weeks
  - Taper over next 4 weeks

**Indomethacin**
- 50 mg tid x 2 weeks
  - Taper over next 4 weeks

Colchicine x 3 months

0.6 mg bid (≥70 kg)
0.6 mg daily (<70 kg)
Chronic pericarditis

Treatment

• Proper treatment for acute pericarditis
  • NSAIDs x 6 weeks, tapering every 2 weeks
  • Colchicine x 3-6 months

• Avoid intense physical activity

• Assess after completion of therapy
  • Resolution of symptoms
  • Normalization of inflammatory markers
What is your management step?

A. Exercise stress echocardiogram
B. Cardiac MRI
C. Oral prednisone x 3 months
D. Ibuprofen 800 mg tid, taper over 6 weeks
E. Ibuprofen 800 mg tid, taper over 6 weeks + colchicine 0.6 mg bid x 3 months
F. Reassurance

- No indication, avoid exercise
- Obtain if diagnosis uncertain
- Avoid early Rx with steroids
- Use NSAIDs + colchicine
- Completely treat acute episode!
- Not yet!

@MayoClinicGIM
42-year-old male

Chronic pericarditis

Incomplete treatment of acute pericarditis is a common cause for chronic pericarditis.

Initial treatment for acute (and chronic) pericarditis includes NSAIDs x 6 weeks + colchicine x 3-6 months.

Avoid glucocorticoids as initial treatment for pericarditis. Avoid intense physical activity during treatment.
A quick word on another cause of sharp pleuritic chest pain…
Costochondritis

- Sharp chest discomfort, can be positional/pleuritic
- Inflammation of costochondral joint, upper>lower joints, typically absent swelling, but can occur (Tietze syndrome)
- Diagnosis = reproducible with palpation
- Treatment = reassurance, acetaminophen and/or NSAIDs, heat/cold, avoidance of aggravating activities
- Stretching activities – doorway stretch, rolled towel stretch

Sharp chest pain Pericarditis mimic

- Sternum
- Cartilage
Case #4
32-year-old female

• 6 months of sporadic palpitations
• “Flip-flopping” in chest
• Multiple times daily, last seconds
• Random, no provoking factors
• Associated with mild dyspnea
• No syncope or chest pain
32-year-old female
“Flip-flopping” in chest

- Non-smoker, rare alcohol & caffeine
- Heart rate 65 bpm
- Blood pressure 115/75 mmHg
- Occasional ectopic beats on exam
- Otherwise normal physical exam
- CBC, electrolytes, TSH normal

@MayoClinicGIM
32-year-old female
“Flip-flopping” in chest

Holter monitor
Sinus rhythm with sinus arrhythmia, average 72 bpm
Frequent supraventricular ectopic beats
500 single PVC’s in a 24-hour period
Post-ectopic pauses, longest 2.2 seconds
“Flip-flops” associated with supraventricular ectopy
32-year-old female
“Flip-flopping” in chest

Normal LV size, EF 65%
Normal RV size and function
Normal valves, no effusion
What is your next step?

A. Exercise stress test
B. Atenolol 25 mg twice daily
C. Metoprolol succinate 200 mg once daily
D. Flecainide 100 mg 2x daily
E. Refer for pacemaker implantation due to sinus node dysfunction
F. Refer for invasive electrophysiology testing and potential ablation
Spectrum of palpitations
General medicine patients

190 patients with palpitations

Etiology of palpitations

- Cardiac: 43%
- Psychiatric: 16%
- Miscellaneous: 10%
- Unknown: 31%

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-fib / flutter</td>
<td>15.8%</td>
</tr>
<tr>
<td>SVT</td>
<td>9.5%</td>
</tr>
<tr>
<td>PVC’s</td>
<td>7.9%</td>
</tr>
<tr>
<td>PAC’s</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

@MayoClinicGIM
# Spectrum of palpitations

## General medicine patients

### Predictors of cardiac etiology

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Patients with cardiac etiology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0</td>
</tr>
<tr>
<td>Description of “irregular heartbeat”</td>
<td>26</td>
</tr>
<tr>
<td>History of heart disease</td>
<td>48</td>
</tr>
<tr>
<td>Event duration &gt;5 min</td>
<td>71</td>
</tr>
</tbody>
</table>

![Bar chart showing the percentage of patients with cardiac etiology based on the number of predictors.](chart)
# Evaluation of palpitations

## Ambulatory monitoring

### Common findings on Holter reports

<table>
<thead>
<tr>
<th>Finding</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus arrhythmia</td>
<td>Common, usually normal&lt;br&gt;More frequent in young &amp; healthy</td>
</tr>
<tr>
<td>Supraventricular ectopy</td>
<td>Includes junctional and atrial premature beats&lt;br&gt;Usually benign and asymptomatic</td>
</tr>
<tr>
<td>Ventricular ectopy</td>
<td>&gt;20,000 PVC’s necessary to cause cardiomyopathy&lt;br&gt;Look for secondary causes</td>
</tr>
<tr>
<td>Pauses</td>
<td>≥3 seconds in sinus rhythm or ≥5 seconds in a-fib is concerning</td>
</tr>
</tbody>
</table>
## Evaluation of palpitations

### Ambulatory monitoring

**Alternative monitoring: Two questions**

1. **How frequent are the spells?**
2. **How symptomatic is the patient?**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>24- or 48-hour Holter monitor</td>
</tr>
<tr>
<td>1-2x weekly, prolonged symptoms</td>
<td>Patient-triggered event (i.e. loop) monitor OR patch monitor</td>
</tr>
<tr>
<td>1-2x weekly, minimal symptoms</td>
<td>Auto-triggered event (i.e. loop) monitor OR patch monitor</td>
</tr>
<tr>
<td>Monthly or less, ± high risk features</td>
<td>Implantable loop recorder</td>
</tr>
<tr>
<td>Possible high-risk arrhythmia</td>
<td>Mobile cardiac outpatient telemetry</td>
</tr>
</tbody>
</table>

@MayoClinicGIM
Evaluation of palpitations
Wearable monitors

- Improve patient engagement
- Increase detection of atrial fibrillation
- More frequent use of anticoagulation
- Limited impact on patient outcomes (yet)
Evaluation of palpitations
Commercial devices

**AliveCor KardiaMobile 6L**
Currently $129

6 lead device, may help with interpreting artifact vs real arrhythmia

Take device diagnoses with a grain of salt

Balance risks/benefit on patient’s stress level
Supraventricular ectopy

Treatment

- Exclude structural heart disease
- If asymptomatic → Observe
- Limit exacerbating factors → OSA, alcohol, stress
- β-blockers
  - 1st line medical therapy
  - Start low dose (metoprolol succinate 25 mg daily)
- 2nd line therapy
  - Calcium channel blockers
  - Anti-arrhythmics, digoxin
What is your next step?

A. Exercise stress test
B. Atenolol 25 mg twice daily
C. Metoprolol succinate 200 mg once daily
D. Flecainide 100 mg 2x daily
E. Refer for pacemaker implantation due to sinus node dysfunction
F. Refer for invasive electrophysiology testing and potential ablation

No indication!
Low dose β-blocker best choice
Dose too high!
Rarely use antiarrhythmic meds
Pauses not worrisome
Not yet, and it shouldn’t be necessary!
32-year-old female
“Flip-flopping” in chest

Remember the predictors for a cardiac etiology of palpitations (male sex, duration >5 minutes, “irregular” heartbeat, known heart disease)!

Pauses <3 seconds and sporadic PVCs are usually not severe enough to cause trouble.

Low dose β-blockers are first line medical treatment for symptomatic supraventricular ectopy.
Summary

• Case #1 → 59-year-old female with exertional chest tightening
• Case #2 → 26-year-old female with palpitations, chest pain, and mitral valve prolapse
• Case #3 → 42-year-old male with chronic pericardial pain
• Case #4 → 32-year-old female with “flip flopping” in chest
Some closing thoughts…
What do you do when all the tests are negative?

1. Reassurance
   - No more cardiac tests
   - No invasive procedures
   - No life-altering heart disease

2. Lifestyle modification
   - Smoking cessation, alcohol limitation
   - Healthy weight, diet, exercise

3. Basic primary cardiovascular prevention

“Your heart is pretty healthy.”
“Let’s keep it that way!”

@MayoClinicGIM
Take home points

1. Always consider the pre-test probability for coronary disease when evaluating a patient with chronic chest pain

2. Mitral valve prolapse is a cause of mitral regurgitation rather than a unique clinical syndrome or an explanation for chronic chest pain or palpitations

3. Ensure patients with chronic pericarditis have been appropriately treated for acute pericarditis

4. Supraventricular ectopy is usually benign and responds to β-blocker therapy, if necessary
QUESTIONS & ANSWERS

geske.jeffrey@mayo.edu
@jeffreygeske

@MayoClinicGIM