When Are “Normal” Coronary Arteries Not Normal? The Role of Vasomotor Reactivity Testing

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November 10, 2016
A 42-year-old woman with no cardiac risk factors comes in for a consultation.

Chest pain for 2.5 years—substernal, occasionally goes into left shoulder and neck—can come on with exertion, but also at rest—simply tries to relax until it goes away.

Has put on 15 pounds because she stopped exercising because of her symptoms and is constantly tired.

Saw another cardiologist ~1 year ago—did a holter, echo, and nuclear perfusion scan—all were normal.

Several ER visits, all unrevealing—stopped going to ER.

Occasionally tearful—physical exam unremarkable.
Is her chest pain angina?

Is her chest pain typical, atypical, or non-cardiac?

Table 1
Clinical classification of chest pain

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Typical angina</td>
<td>Meets three of the following characteristics</td>
</tr>
<tr>
<td>(definite)</td>
<td>Substernal chest discomfort of characteristic quality and duration</td>
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<td></td>
<td>Provoked by exertion or emotional stress</td>
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<td></td>
<td>Relieved by rest and/or GTN</td>
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<tr>
<td>Atypical angina</td>
<td>Meets two of the above characteristics</td>
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<tr>
<td>(probable)</td>
<td>Non-cardiac chest pain</td>
</tr>
<tr>
<td></td>
<td>Meets one or none of the above characteristics</td>
</tr>
</tbody>
</table>

Possible areas of radiating pain: neck, jaw, upper abdomen, shoulders and arms

Diamond AG. J Am Coll Cardiol 1983;1:574-575
Complains of angina-like symptoms

GERD—Given a PPI

Asthma—Given an inhaler

Stress test

Positive

Angiogram Positive

Obstructive CAD—stent

Negative

Crazy—Given Xanax

Definitely Crazy—Referred to psych
Angina is very common

- An estimated 10 million Americans have angina.

- At least 20% of patients clinically referred for coronary angiography will have no significant obstructive CAD on angiography.

- Women >> men (across all presentations).

- These patients are “reassured” that their chest pain is non-cardiac.

Bugiardini et al. JAMA 2005;293:477-484
Daly et al. Circulation 2006;113:490-498
Women presenting with symptoms suggestive of angina, but having normal appearing coronaries on angiography

- Frequently (>50%) had evidence of endothelial dysfunction
- Frequently (~60%) had evidence of microvascular dysfunction

**NOT A BENIGN PATHOLOGY**

- Associated with long-term CV events and death
- Ongoing angina and functional disability
- Repeat testing, hospitalization, and economic burden

**WISE Study (Women's Ischemic Syndrome Evaluation)**

- Sponsored by AHA/NHLBI
- Four-center project, ~1000 women (mean age 59±12 years) enrolled. Women were presenting with suspected ischemia and were referred for elective coronary angiography.

Reis et al. J Am Coll Cardiol 1999; 33: 1469-1475
Pepine et al. JACC 2010; 55: 2825-32
Shaw et al. Circulation 2006; 114: 894-904
How Do We Evaluate These Patients?

Four measures of coronary vascular autoregulation

- Endothelial-dependent macrovascular function (Ach, QCA)
- Endothelial-independent macrovascular function (nitro, QCA)
- Endothelial-dependent microvascular function (Ach, CFR, CBF)
- Endothelial-independent microvascular function (Adenosine, CFR, IMR)

Limitations

- Drugs are not purely endothelial dependent/independent
- Cut-offs vary (QCA, CFR/IMR) (Differentiating from vasospasm)
- Drugs may have different effects at different doses
- Different devices used (Doppler wire, pressure wire, chest pain/EKG)
- Often only one vessel studied
- IVUS often not used (knowing what it looks like inside is important!)
- We don’t know what normal is (lack of controls)
- Focus on women
All patients undergo

- Coronary angiogram
- Endothelial function testing
- Microvascular testing
- FFR
- IVUS
We slowly inject 20 µg acetylcholine directly into the left coronary artery.

Unless there is significant bradycardia or severe vasoconstriction, up to 200 µg acetylcholine is subsequently administered.

After each injection, coronary angiography is performed and QCA is performed offline.

Define endothelial dysfunction as a decrease in the epicardial coronary artery diameter by >20% compared with baseline.
Endothelial Dysfunction - Normal
Endothelial Dysfunction
Place a coronary pressure-temperature sensor coronary wire

Calculate resting mean transit time by injecting 3mL of room-temperature saline down the coronary artery 3x

Administer 140 mcg/kg/min IV adenosine to induce maximal hyperemia

Calculate hyperemic mean transit time by same method

Determine CFR and IMR

Defined microvascular dysfunction as an IMR ≥ 25
IMR is based on Ohm’s law ($\Delta P/F = R$)

- FFR = $P_d / P_a$ at hyperemia
- CFR = hyperemic $T_m$ / resting $T_m$
- IMR = $P_d$ at hyperemia × hyperemic $T_m$
IMR: $63 \times 0.52 = 32.8$
CFR: $1.30/0.52 = 2.5$
There is more data regarding CFR than IMR.

CFR assumes a normal epicardial vessel, whereas measures of IMR are independent of the epicardial vessel.

CFR is variable and affected by hemodynamic conditions (such as heart rate, blood pressure, and contractility), predominately because of the reliance on resting flow.

IMR uses only hyperemic flow, which is less variable.

$\text{CFR}_{\text{flow}}$ compared with $\text{CFR}_{\text{thermo}}$ has been shown to underestimate the true coronary flow.

Cut-offs somewhat variable:
- $\text{CFR} < 2.0$ to $2.5$, $\text{IMR} > 20$ to $25$

Ng et al. Circulation 2006; 113: 2054-2061
Fearon et al. Circulation 2003; 108; 2198-2200
No sex difference in microvascular dysfunction, but CFR lower in women than men
Women have a shorter resting mean transit time

On multivariable analysis, female sex was independently associated with both a lower CFR and shorter resting mean transit time.

Sex was not an independent predictor of IMR or hyperemic mean transit time.

Shorter mean transit time = higher resting coronary flow

Angiography + physiology doesn’t always tell the whole story

WAIT...

WHAT DID YOU SAY?
68 yo man with hypertension and tobacco history

Typical angina

2 negative stress echocardiograms
FFR in LAD
49 yo woman with progressive exertional angina

No ischemia on stress testing
Echo-lucent half moon sign (halo) felt to be pathognomonic, although not 100% sensitive.

≥ 10% systolic compression

Lin, Tremmel et al. J Am Heart Assoc 2013;2:e000097
Myocardial bridging

- Present in ~1/3 of population by autopsy (<5% by angiography), mostly LAD
- Occurs in almost 60% of patients with chest pain and non-obstructive CAD
- Often associated with endothelial dysfunction
- Symptoms typically do not develop before the third decade
- Challenge in distinguishing hemodynamically significant vs. incidental
Compressive Effects Extend into Diastole
dFFR with Dobutamine Stress
Majority have occult coronary abnormalities

Cross-over of abnormalities

N=139

Angina in the absence of obstructive CAD is common

Reassurance doesn’t make these patients feel better, nor does it improve their prognosis

Consider testing for an occult vascular abnormality

- Endothelial Dysfunction
- Microvascular Dysfunction
- Diffuse plaque
- Myocardial bridge

Can help guide therapy, reduce symptoms, decrease repeat visits/tests/hospitalizations/costs, and hopefully improve prognosis
Patient Population

- Initial study looked at the overall cohort (n=139)

- Sex differences studies had up to 181 subjects (n=137 (76%) women and 44 (24%) men)

- Excluded patients with
  - ≥50% stenosis on coronary angiography
  - acute coronary syndrome
  - prior heart transplantation
  - prior percutaneous coronary intervention or coronary artery bypass grafting
  - renal insufficiency (creatinine> 1.5 mg/dL)
  - abnormal ejection fraction (<55%)
  - presence of another likely explanation of angina such as pulmonary hypertension, hypertrophic cardiomyopathy, or valvular heart disease
All patients had stable angina, with 61.8% having typical symptoms and the remainder having atypical symptoms.

- Typical angina (64.3% women vs. 54.5% men, p=0.3)

Stress testing:

- 72.9% had had an abnormal stress test
- 23.2% had had at least 1 normal stress test, but were still referred for coronary angiography because of persistent and concerning symptoms
- Six patients were referred directly to angiography without stress testing
SAQ before and after surgical unroofing

Sex Differences in Atheroma Burden and Vascular Function Abnormalities

Han et al. Eur Heart J 2008;29:1359-1369