Understanding the Pathophysiology of Ischemic Chronic Heart Disease: Stable Angina the Tip of the Iceberg

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Ischemic Chronic Heart Disease

Flow-Limiting Lesion

Myocardial Ischemia

Myocardial O$_2$ supply

Myocardial O$_2$ demand

Physical /emotional stress

Blood pressure
• Heart Rate
• Contractility

Relief

Nitroglycerin
• Interruption of activity

Angina
Angina Prevalence

Murphy, et al. Heart 2006 92: 1047-1054
Angina Incidence

Murphy, et al. Heart 2006 92: 1047-1054
The Euro Heart Survey of Stable Angina set out to prospectively study the presentation and management of pts with stable angina as first seen by a cardiologist in Europe. 3779 patients were included in the analysis.

### Clinical details of patients presenting with stable angina

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 3779)</th>
<th>North (n = 521)</th>
<th>West (n = 951)</th>
<th>Central (n = 1341)</th>
<th>Med (n = 966)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>2197/3779 58%</td>
<td>315/521 60%</td>
<td>489/951 51%</td>
<td>784/1341 58%</td>
<td>609/966 63%</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>61 (11)</td>
<td>62 (10)</td>
<td>61 (10)</td>
<td>60 (13)</td>
<td>64 (11)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>652/3666 18%</td>
<td>74/511 14%</td>
<td>142/910 16%</td>
<td>209/1309 16%</td>
<td>227/936 24%</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2267/3676 62%</td>
<td>245/512 48%</td>
<td>485/901 54%</td>
<td>921/1321 70%</td>
<td>616/942 65%</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>1843/3174 58%</td>
<td>247/473 52%</td>
<td>334/710 47%</td>
<td>728/1125 65%</td>
<td>534/866 62%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>819/3553 23%</td>
<td>100/500 25%</td>
<td>222/762 29%</td>
<td>277/1326 21%</td>
<td>220/965 23%</td>
</tr>
<tr>
<td>Family history</td>
<td>1347/3161 43%</td>
<td>223/453 49%</td>
<td>361/745 48%</td>
<td>474/1119 42%</td>
<td>289/844 34%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>267/3779 7%</td>
<td>13/521 3%</td>
<td>67/951 7%</td>
<td>114/1341 9%</td>
<td>73/966 8%</td>
</tr>
<tr>
<td>CVA or TIA</td>
<td>197/3779 5%</td>
<td>22/521 4%</td>
<td>52/951 5%</td>
<td>69/1341 5%</td>
<td>54/966 6%</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>313/3779 8%</td>
<td>47/521 9%</td>
<td>90/951 9%</td>
<td>98/1341 7%</td>
<td>78/966 8%</td>
</tr>
<tr>
<td>Chronic hepatic disease</td>
<td>72/3779 2%</td>
<td>1/521 0.2%</td>
<td>6/951 0.6%</td>
<td>42/1341 3%</td>
<td>23/966 3%</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>54/3779 1%</td>
<td>1/521 0.2%</td>
<td>10/951 1%</td>
<td>17/1341 1%</td>
<td>26/966 3%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>61/3779 2%</td>
<td>9/521 2%</td>
<td>21/951 2%</td>
<td>13/1341 1%</td>
<td>18/966 2%</td>
</tr>
</tbody>
</table>

CVA, cerebrovascular accident; TIA, transient ischaemic attack; Med, Mediterranean.

**Daly, et al. European Heart Journal 2005; 26: 996–1010**
Obstructive lesion

Depletion of myocardial energy stores

Decreased coronary flow reserve

LV dysfunction

ECG changes

Angina pectoris

Time

Obstructive lesion

Decreased CFR

Depletion of myocardial energy stores

LV dysfunction

ECG changes

Time

Angina pectoris
Experimental vs. Clinical Stenosis Severity


Diagnostic Performance of QCA, QCT, CCA, CTCA vs. FFR

Meijboom, et al. JACC 2008; 52:636-43
Coronary Function vs. Anatomy With Diffuse CAD and Remodeling

A

1. Blood Flow

No stenosis  CFR = 4.0
87% stenosis  CFR = 1.0
63% stenosis  CFR = 3.4
Diffuse no stenosis
IVUS 38%  CFR = 1.4
Diffuse + 60% Artgm
IVUS 75%  CFR = 1.0
Diffuse + 62% Artgm
IVUS 75% & adaptive remodeling  CFR = 3.5

B

Coronary Flow Reserve vs. % Diameter Stenosis

Gould KL. JACC Imaging 2009; 2: 1009-23
At maximum vasodilation

\[ Q_{\text{max, normal}} = \frac{(P_a - P_v)}{R_{\text{min}}} \]

At stenosis

\[ Q_{\text{max, stenosis}} = \frac{(P_d - P_v)}{R_{\text{min}}} \]

\[
FFR = \frac{(P_d - P_v)}{(P_a - P_v)} = \frac{P_d}{P_a}
\]

Pijls and De Bruyne. Heart 1998;80:539–542
Coronary Function Versus Stenosis and Outcome

Boden, et al.  

Tonino, et al.  
Obstructive lesion

Decreased CFR

Depletion of myocardial energy stores

LV dysfunction

ECG changes

Time

Angina pectoris
Glucose and Fatty Acid Metabolism in the Aerobic Heart

Glucose and Fatty Acid Metabolism During Myocardial Ischemia/Reperfusion

Obstructive lesion
Decreased CFR
Depletion of myocardial energy stores
LV dysfunction
ECG changes
Angina pectoris

Time
Na\(^+\) and Ca\(^{++}\) Homeostasis in Myocardial Ischemia

Maier LS. J Cardiovasc Pharmacol 2009; 54:279-86
**Na+ Handling and LV Dysfunction in Myocardial Ischemia**

- **O₂ and ↓ATP**
- **↓O₂ and ↓ATP**
- **Late I_{Na}**
- **↑Na+**
- **↑Ca++**
- **NCX**
- **Electrical instability**
- **Mitochondrial dysfunction**

- **LV Systolic Dysfunction**
- **Extravascular compression**
- **↑LVEDP**
- **↑LV Wall Tension**
- **↑Myofilament activation**

*Maier LS. J Cardiovasc Pharmacol 2009; 54:279-86*
Obstructive lesion

Decreased CFR

Depletion of myocardial energy stores

LV dysfunction

Angina pectoris

ECG changes

Time

Obstructive lesion

Decreased CFR

Depletion of myocardial energy stores

LV dysfunction

Angina pectoris

ECG changes

Time
An ischemic episode is defined as ≥ 1 mm horizontal or downsloping ST segment depression lasting at least one minute and separated from other episodes by at least one minute (1X1X1 rule).

Three quarters of ischemic episodes are asymptomatic!

*Deedwania and Stone. Curr Probl Cardiol 2001;26:680-727*
Prognostic Significance of Ambulatory Ischemia in Stable CAD

- **Multicenter Study of Myocardial Ischemia (MSMI) (n=936)**
  No increase in cardiac events associated with ambulatory ischemia (silent or symptomatic) in stable patients 1 to 6 months after MI or UA.

  *JAMA 1993;269:2379-85*

- **The Total Ischemic Burden Bisoprolol Study (TIBBS) (n=520)**
- **Atenolol and Silent Ischemia Study (ASIST) (n=306)**
- **Asymptomatic Cardiac Ischemia Pilot Study (ACIP) (n=496)**
  Ambulatory ischemia is associated with adverse outcome (subjective end points such as revascularization and aggravation of angina were included).


- **Angina Pectoris Study In Stockholm (APSIS)(n=686)**
  Treatment reduces ambulatory ischemia but does not influence prognosis.

  *Am J Cardiol 1999;84:1151–7*

- **Total Ischemic Burden European Trial (TIBET)(n=682)**
  Recording of ischemic events in Holter monitoring fails to predict cardiac events (hard or soft).

  *Eur Heart J 1996;17:104–12*
Calculation of CAD Probability

45 year-old asymptomatic man with no risk factors

45 year-old asymptomatic man with hypercholesterolemia, hypertension, and diabetes

55 year-old man with typical angina

45 year-old man with atypical chest pain

+ST

-ST

Clinical pretest probability of CAD present

Posttest probability of CAD present

Duke Exercise Score

ST-segment deviation during exercise

Ischemia-reading line

Angina during exercise

Prognosis

Duration of exercise


Obstructive lesion
Decreased CFR
Depletion of myocardial energy stores
LV dysfunction
ECG changes
Angina Pectoris

<table>
<thead>
<tr>
<th>Classic (Typical)</th>
<th>Atypical, Noncardiac</th>
</tr>
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<tbody>
<tr>
<td>Sensations in chest of squeezing, heaviness, pressure,</td>
<td>Pain that is pleuritic, sharp, pricking, knife-like,</td>
</tr>
<tr>
<td>weight, vise-like aching, burning, tightness</td>
<td>pulsating, lancinating, choking</td>
</tr>
<tr>
<td>Radiation to shoulder, neck, jaw, inner arm, epigastrium</td>
<td>Involves chest wall; is positional, tender to palpation;</td>
</tr>
<tr>
<td>(can occur without chest component); band-like</td>
<td>can be infra-mammary; radiation patterns highly variable</td>
</tr>
<tr>
<td>discomfort</td>
<td></td>
</tr>
<tr>
<td>Relatively predictable</td>
<td>Random onset</td>
</tr>
<tr>
<td>Lasts 3–15 min</td>
<td>Lasts seconds, minutes, hours, or all day</td>
</tr>
<tr>
<td>Abates when stressor is gone or nitroglycerin is taken</td>
<td>Variable response to nitroglycerin</td>
</tr>
</tbody>
</table>

Classification and Severity of Angina

**Class I**
No angina with ordinary physical activity (e.g., walking, climbing stairs)
Angina with strenuous or prolonged exertion

**Class II**
Early-onset limitation of ordinary activity (e.g., walking rapidly or walking >2 blocks; climbing stairs rapidly or climbing >1 flight); angina may be worse after meals, in cold temperatures, or with emotional stress

**Class III**
Marked limitation of ordinary activity

**Class IV**
Inability to carry out any physical activity without chest discomfort
Angina occurs during rest

Seattle Angina Questionnaire

- **Anginal Stability**: a measure of whether a patient’s symptoms are changing over time

- **Anginal Frequency**: a measure of how often a patient is having symptoms now

- **Physical Limitation**: a measure of how much a patient’s condition is hampering his ability to do what he wants to do

- **Treatment Satisfaction**: a measure of how well a patient understands her care and what she thinks of it

- **Quality of Life**: a measure of the overall impact of a patient’s condition on a patient’s interpersonal relationships and state of mind

*Spertus, et al. J Am Coll Cardiol 1995;25:333-41*
Prognostic utility of the Seattle Angina Questionnaire (SAQ) for patients with CAD. Pts were enrolled in a prospective cohort study from 6 VA General Internal Medicine Clinics. All pts reporting CAD who completed a SAQ and had 1 year of follow-up were analyzed (n=5558). The primary outcome was 1-year all-cause mortality.

Angina Pectoris: Nervous and Neurohumoral (?) Pathways

Angina pectoris

Somato sensible cortex

Thalamus (coordination and integration)

Spinothalamic tract

Dorsal horn neurons
Dorsal root ganglion

Cardiac sensory fibers (extrinsic cardiac ganglia)

Intrinsic cardiac neurons (intrinsic cardiac ganglia)

Myocardial ischemia

Glucocorticoid-Activated Descending Pathways from the Amygdala

- Anxiety
- Depression

Circulating glucocorticoids

Neurogenic Hypothesis of Cardiac Ischemic Pain

Ischemia stimulates sensory nerve endings of the heart to release neuropeptides and neurotransmitters.

Initiation and aggravation of myocardial injury in ischemic areas, which may involve the whole myocardium.

Nociception of CNS might also be sensitized and increased, resulting in more efferent impulses and more secretion of nerve endings.

The nerve endings in the injury tissue are sensitized and more and stronger nociceptive stimuli are produced, and ascend to CNS.

SCS and Refractory Angina: Review and Meta-Analysis of RCTs

7 RCTs were identified in a total of 270 refractory angina patients

Exercise capacity

Myocardial O₂ Supply/Demand Ratio

Pain perception

Sympathetic tone

Conclusions

- Angina pectoris is considered to be the symptomatic result of chronic ischemic heart disease, which is characterized by the presence of obstructive lesions in the coronaries leading to a decrease in coronary flow reserve.

- In outpatients with ischemic chronic heart disease, the patients’ health status (symptoms, physical function, and quality of life) is a strong predictor of subsequent mortality and admission for acute coronary syndrome.

- Neurogenic inflammation and neurogenic activity might participate in the pathophysiological processes following myocardial ischemia and contribute to the myocardial ischemic injury.

- Antiaginal interventions could not only relieve the pain symptoms, but also block nociception of body and neurogenic reaction induced by ischemia, thereby extenuating ischemic myocardial injury and offering myocardial protection.