Coronary Microvascular Dysfunction in Stable CAD

Carl J. Pepine MD, MACC, FESC
University of Florida
Gainesville, FL.
## Disclosure of Financial Relationships

<table>
<thead>
<tr>
<th>Grant/Research Support:</th>
<th>Amarin Pharma, Amorycyte, Angioblast/Mesoblast, Baxter Healthcare, Bayer HealthCare, Daiichi-Sankyo, Gilead, GlaxoSmithKline, Lilly, Merck, NIH/NHLBI, Pfizer, sanofi-aventis, Viron Therapeutics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speakers Bureau:</td>
<td>None</td>
</tr>
<tr>
<td>Stock Shareholder:</td>
<td>None</td>
</tr>
<tr>
<td>Other Financial or Material Support:</td>
<td>Holds two patents with the University of Florida.</td>
</tr>
</tbody>
</table>

Carl J. Pepine, MD, MACC, FESC
Inflammation and microcirculation

**Coronary Microvascular Dysfunction (CMD) in Stable CAD**

Talking Points:

- Role of CMD in stable ischemic syndromes?
  - Flow-limiting stenosis and limitations
  - Historical considerations for CMD
  - Prevalence of CMD
- Links with CV risk factors/ inflammation?
- Is CMD a predictive for adverse outcomes?
- Can CMD be modified/ is it reversible?
- Implications and future directions?
What Causes Stable CAD?


• Transient myocardial ischemia underlies stable CAD syndromes (IHD).

• Pathologic studies established *atherosclerosis* in the overwhelming majority of cases. Angiographic data assumed this to mean “flow-limiting stenosis” (e.g. obstructive CAD) which became the sine qua non for stable CAD.

• Without obstructive CAD, management of patients with angina and other findings of SIHD represents a considerable challenge for which there is virtually no reliable evidence-base.
  
  — Link between symptoms and obstructive stenosis is so ingrained that many physicians doubt that a patient may have symptoms and/or signs of ischemia in the absence of such a stenosis.

  — Often labeled “atypical” or “false positive results” /many are women.

• But most patients thought to have “stable IHD” have no obstructive CAD.
Obstructive CAD Prevalence Among Stable Patients Undergoing Elective Coronary Angiography by Indication and Age*

Anderson and Pepine. *Harrison’s Online*, Chapter 238; 2009.

*ACC’s National Cardiovascular Data Registry (n >2 million patients)
What Causes Stable IHD (SIHD)?

- Clinical “paradox of normal selective coronary arteriograms” was first reported by Likoff, et al (N Eng J Med 1967) in 15 women with stable angina and abnormal stress tests “considered to have unmistakable CAD”. They hypothesized a coronary “microvascular defect”.

- Reports followed documenting ischemia by different methods and microvascular abnormalities in other organs (e.g. eye, nerve, kidney, etc.).

- To explain inappropriate coronary microcirculation responses to vasodilators Cannon, et al suggested “reduced vasodilator reserve of small coronary arteries” (1983) and then “microvascular angina” (1988).

- In contrast to ischemia associated with obstructive CAD, LV wall motion was generally preserved.
What Causes Stable IHD (SIHD)?

These concerns led to the NHLBI-WISE in 1996:

- Two-thirds of the initial consecutive cohort (n=936) with stable angina/findings suggesting IHD had no obstructive CAD (e.g. ≥50%).
- Not a benign syndrome:
  - At 5-yrs 13.1% death/MI (or 2.6%/yr)
  - At 9-yrs 20% have died, of these, 115 (62%) were CV deaths; 25% of all and CV deaths occurred in women without obstructive CAD (3/4 of their angios read as “NCA”).
- ~50% of those tested had microvascular dysfunction.
- >80% with “NCA” had athero/plaque by IVUS.
- >95% had multiple CAD risk factors: most had endothelial dysfunction.

Ideal model to study coronary microvascular dysfunction (CMD) in patients with ischemia (no collateral flow, PCI).
Obstructive coronary artery disease by examination year among stable angina patients referred for angiography

Men

Women

Jespersen L, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risk of major adverse CV events. *Eur Heart J* 2012;33:734-44.
Stable angina pectoris with no obstructive CAD is associated with increased risks of major adverse CV events

A case for CMD: Evidence against flow-liming stenosis as the reference standard for SIHD

– **Majority of patients** with “stable CAD” (e.g. chronic angina) and signs of ischemia) undergoing angiography have *no flow limiting stenosis*\(^1-3\).

– Even when obstructive stenosis documented, there is often *wide variability* in symptoms/effort tolerance, as well as ischemic responses to stress testing making *lack of concordance* the rule\(^4\).

– High degree of *scatter* between *stenosis severity and flow*\(^5,6\).

– Conversely, *reduced flow responses*, to a variety of stressors in regions perfused by *non-stenotic vessels*, are well documented\(^7\).

– *Highly variable clinical outcomes* after *stenosis* relief as meta-analyses fail to document differences in outcomes comparing medical therapy with PCI\(^8\).

Coronary macro and microvascular systems
Confocal image (overview, maximal intensity plot) of a proteolytically isolated microvascular network (LV bovine myocardium) after labeling for vWF in EC (green) and α-SMC-actin (red) in pericytes; art= arterioles, ven= venules.

Myocardial blood flow (PET) with insulin resistant states of different severity in subjects without obstructive CAD

Schelbert HR. *Heart* 2012;98:592-600

![Graph showing data on myocardial blood flow (MBF) and cold pressor test (ΔMBF) for different insulin resistance states.]

**Adenosine hyperaemia**

- IS, normal insulin resistance
- IR, normoglycemic insulin resistance
- IGT, impaired glucose tolerance
- DM, type 2 diabetes
- DM+HTN, diabetes with hypertension

**Cold pressor test**

- IS, n=19
- IR, n=47
- IGT, n=25
- DM, n=21
- DM+HTN, n=8

* denotes statistical significance.
Inflammation is Related to CFR (PET) in Asymptomatic Male Twins
Vaccarino JACC. 2011;57:1271-79
N=210  ~50% of the women without obstructive CAD tested had CFR <2.5
Athero RF conditions, including inflammatory markers explained only ~ 20%
of the variability in CFR
Detection of Microvascular Disease: Risk Factor Analysis vs PET


CFR (dipyridamole PET) pts with angina/normal angiograms plus controls and number of CV risk factors (NRF).

- 85% of pts with ≥5 RFs had ↓CFR and 100% of those with <2 RFs had normal CFR.
- In about 2/3 of pts, angina can be explained by ↓CFR as RFs had cumulative negative effect on CFR.
- RF analysis enables estimation of individual probability of CMD in most patients.
- CFR measurements recommended for pts with intermediate number of RFs.
CMD as Microvascular Spasm:
High prevalence of pathologic responses to acetylcholine testing (2-200ug) in patients with stable angina and unobstructed coronary arteries

Ong, P, et al., JACC 2012;59;655-62

Patients with chest pain and suspected CAD (n=376)

Eligible patients according to inclusion/exclusion criteria (n=304)

Diagnostic coronary angiography

Obstructive CAD (≥50% stenosis) (n=139; 46%)

Narrowings >20-49% (n=21; 7%)

Normal coronary arteriogram (0-20% narrowings) (n=144; 47%)

ACH-test (n=124; 86%)

No ACH-test (n=20; 14%)

Abnormal coronary vasomotion (n=77; 62%)

Epicardial spasm (n=35; 45%)

Microvascular spasm (n=42; 55%)
Macro versus Microvascular Spasm:
High prevalence of pathologic response to acetylcholine testing (2-200ug) in patients with stable angina and unobstructed coronary arteries

Ong, P, et al., JACC 2012;59;655-62
## Prognosis and Coronary Microvascular Dysfunction (CMD): Stable Coronary Syndromes: Mostly with obstructive CAD

<table>
<thead>
<tr>
<th>Author year</th>
<th>N</th>
<th>Population</th>
<th>Method</th>
<th>Outcome measure</th>
<th>Follow-up</th>
<th>CMD Outcome Predictor Univariate</th>
<th>CMD Outcome Predictor Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Britten 2004</td>
<td>120</td>
<td>Post PCI/mild CAD</td>
<td>Intracoronary Papav. or Ado-CFR IC Doppler flow wire</td>
<td>Cardiac death, ACS, revasc., stroke</td>
<td>6.5±3 yrs. (14-125 mos.)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Schindler 2005</td>
<td>72</td>
<td>CAD risk factors without flow-limiting stenosis</td>
<td>CPT-MBF increase with $^{13}$N-NH$_3$ PET</td>
<td>CV death, ACS, MI, PCI/CABG, stroke, PTA</td>
<td>66± 8 mos.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rigo 2007</td>
<td>86</td>
<td>CAD, LAD 51-75% stenosis</td>
<td>Vasodilator LAD CFR, Doppler /TTE</td>
<td>Non-fatal MI</td>
<td>30 mos. 14 median</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nemes 2008</td>
<td>397</td>
<td>Hospitalized, angina, mostly sever CAD, undergoing TEE for AA</td>
<td>Vasodilator LAD CFR, Doppler /TEE</td>
<td>CV death, HF. thrombosis</td>
<td>41±12 mos.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Herzog 2009</td>
<td>229</td>
<td>Suspect CAD/66% had sever CAD</td>
<td>Vasodilator CFR with $^{13}$N-NH$_3$ PET</td>
<td>CV death, nonfatal MI, hospitalization, PCI/CABG</td>
<td>5.5±2.1 yrs.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tio 2009</td>
<td>344</td>
<td>Severe CAD, not revasc. candidates, LV systolic dysfunction</td>
<td>Vasodilator CFR with $^{13}$N-NH$_3$ PET</td>
<td>Cardiac death</td>
<td>85 mos. (1–138)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cortigiani 2010</td>
<td>1,660</td>
<td>Chest pain, Normal DSE</td>
<td>Vasodilator LAD CFR, Doppler /TTE</td>
<td>Death, MI, revasac.</td>
<td>19 mo. median</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ziadi 2011</td>
<td>677</td>
<td>Most had sever CAD</td>
<td>Vasodilator CFR with $^{82}$Rb PET</td>
<td>CV death, nonfatal MI</td>
<td>387 ds. (375–416)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
CMD (LAD CFR) by Echo-Doppler and Prognosis: Chest pain with normal DSE
Cortigiani, et al AJC 2010;106;1703-08

### Annual Event Rates (death and non-fatal MI)

<table>
<thead>
<tr>
<th>Subjects at risk</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (years)</td>
<td>Events %</td>
<td>$X^2$</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>89.5</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

### Annual Revascularization Rates

<table>
<thead>
<tr>
<th>Subjects at risk</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (years)</td>
<td>Revascularizations %</td>
<td>$X^2$</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>76.1</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

Cortigiani, et al AJC 2010;106;1703-08
## Prognosis and Coronary Microvascular Dysfunction (CMD): Stable Coronary Syndromes (Women with angina/ischemia and no obstructive CAD)

<table>
<thead>
<tr>
<th>Author year</th>
<th>N</th>
<th>Population</th>
<th>Method</th>
<th>Outcome measure</th>
<th>Follow-up</th>
<th>CMD Outcome Predictor Univariate</th>
<th>CMD Outcome Predictor Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepine 2010</td>
<td>189</td>
<td>Women with angina/ischemia (WISE), most without severe CAD</td>
<td>Intracoronary Ado-CFR Doppler flow wire</td>
<td>Death, nonfatal MI, nonfatal stroke, HF hospitalization</td>
<td>5.4 yrs. (mean)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Balazs 2011</td>
<td>45</td>
<td>Women with angina/ischemia, no obstructive CAD</td>
<td>Vasodilator CFR, Doppler /TEE, TTE</td>
<td>Death, CV hospitalization</td>
<td>102±26 mos. 113 median</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Coronary Microvascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia

Results From the National Heart, Lung and Blood Institute WISE (Women’s Ischemia Syndrome Evaluation) Study

Carl J. Pepine, MD,* R. David Anderson, MD,* Barry L. Sharaf, MD,† Steven E. Reis, MD,‡ Karen M. Smith, MD,* Eileen M. Handberg, PhD,* B. Delia Johnson, PhD,‡ George Sopko, MD, MPH,§ C. Noel Bairey Merz, MD||

Gainesville, Florida; Providence, Rhode Island; Pittsburgh, Pennsylvania; Bethesda, Maryland; and Los Angeles, California
CFR and Event-Free Survival in WISE

Event-Free Survival: Freedom from nonfatal MI, HF hospitalization, stroke or death 5.4 yrs follow-up
## Table 3  Decreasing LogCFR and Risk for Adverse Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major adverse outcome*</td>
<td>1.16</td>
<td>1.04–1.30</td>
<td>0.009</td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke, or hospital stay for CHF</td>
<td>1.15</td>
<td>1.02–1.30</td>
<td>0.019</td>
</tr>
<tr>
<td>CV death, nonfatal MI, or hospital stay for CHF</td>
<td>1.18</td>
<td>1.03–1.36</td>
<td>0.018</td>
</tr>
<tr>
<td>Women without obstructive CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major adverse outcome*</td>
<td>1.20</td>
<td>1.05–1.38</td>
<td>0.008</td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke, or hospital stay for CHF</td>
<td>1.19</td>
<td>1.03–1.37</td>
<td>0.020</td>
</tr>
<tr>
<td>CV death, nonfatal MI, or hospital stay for CHF</td>
<td>1.23</td>
<td>1.03–1.47</td>
<td>0.021</td>
</tr>
</tbody>
</table>

## Table 4  Multivariate Modeling of Major Events

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Log CFR</td>
<td>1.15 (1.02–1.30)</td>
<td>0.018</td>
<td>1.13 (1.004–1.27)</td>
<td>0.043</td>
<td>1.14 (1.01–1.29)</td>
<td>0.038</td>
</tr>
<tr>
<td>SBP</td>
<td>1.02 (1.005–1.04)</td>
<td>0.011</td>
<td>1.02 (1.004–1.04)</td>
<td>0.012</td>
<td>1.02 (1.001–1.04)</td>
<td>0.035</td>
</tr>
<tr>
<td>Log CAD severity</td>
<td>—</td>
<td>—</td>
<td>1.68 (0.98–2.88)</td>
<td>0.058</td>
<td>1.61 (0.92–2.81)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.00 (0.96–1.04)</td>
<td>0.90</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.44 (0.65–3.20)</td>
<td>0.37</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.22 (0.60–2.46)</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Independent prognostic value of CFR in women with chest pain and negative coronary angiograms (SZEGED study)

Logistic regression model identified only CFR as an independent predictor of risk (HR 2.77, 95% CI 1.27 to 6.25, p <0.05).
TIMI Frame Count as an Index of CMD: Adverse Outcomes in WISE 9 yr follow-up

$P=0.004, N=315$: Adverse event rates compared between patients in the various TFC tertiles (TFC <28 Black, 29-37 Red, and >37 Green)
IS CMD Reversible?

CFR improves in:
- Hypercholesterolemic pts with a statin.
- HTN pts reaching BP goals with several drugs.
- Aortic Stenosis pts with LVH 6 mths after AVR.
- Stable CAD (angina/ischemia) pts?
Effects of Metformin on Microvascular Function and Exercise Tolerance in Women With Angina and Normal Coronary Arteries

Jadhav S, et al. JACC. 2006;48:956-63
Investigated the RAS in stable angina/ischemia without obstructive CAD: WISE substudy.

Women with CMD (CFR<3.0, ado) randomized to either ACE-I (quinapril 40-80 mg/d) or placebo and 61 completed 16-wks treatment with repeat CFR measurements. Treatment was well tolerated.

**Primary outcome:** CFR improved more with ACE-I than placebo \((P < 0.02)\).
**Secondary outcome:** Symptoms (SAQ) improved more with ACE-I than placebo \((P= 0.037)\) and CFR increase was associated with less angina \((P= 0.008)\).

CMD improves with ACE-I in women with signs/symptoms of ischemia without obstructive CAD. CMD improvement is associated with reduction in angina. The beneficial response was greatest in women with lower baseline CFR values, suggesting that the RAS may be more involved among patients with more severe microvascular defects.
Effects of PDE-5 Inhibition in Women with Coronary Microvascular Dysfunction

Ivabradine improves CFR in patients with stable CAD

Nebivolol improves CFR in patients with stable CAD


Control
N=10, No CAD

CAD
N=8, Post stenting

*p<0.05, **p<0.01
Endothelial Stem/Progenitor Cell Number and Function Predicts CFR: Potential biomarker for CMD among women with angina and no obstructive CAD

Endothelial S/P cells, identified by CD34+ expression, and circulating endothelial cells (CECs) reflect degree of endothelial injury and potential to participate in vascular repair.
We hypothesized that number and function of circulating S/P or CECs could serve as biomarkers for CMD.

Peripheral blood samples from women (n=32) with angina and ischemia without obstructive CAD and healthy controls (n=10) assessed for:
• Number of CD34+ cells (FACS)
• CD34+ cell function (migration towards SDF-1) and bioavailable NO.
• CECs identified by monoclonal antibody to CD146.
• Findings examined in a multivariable model to predict CFR.
Results: Women with CMD (CFR ≤2.5) had lower numbers of CD34+ cells vs. controls and these numbers correlated with migration towards SDF-1 (r=0.47, p =0.05). The final model predicted CFR (p=0.0193) as well as CEC number (p=0.0101). The HR*SBP product (p=0.0264), and CEC*CD34+ Migration Product (p=0.0144) were independent predictors. Interestingly none of NO variables, either alone or in combination with cell number or function variables, contributed to CFR prediction.

Summary/Conclusion: Number of circulating CD34+ cells are decreased in symptomatic women with CMD. CD 34+ function (migration towards SDF-1), CEC number, double product, and CEC*CD34+ Migration Product independently predicted CFR.

Thus circulating cells predict CMD and may provide mechanistic insights.
Bone Marrow-CNS-Coronary Microvascular Connections: Hypothetical role in CMD associated with stable CAD

CAD Risk Factors
- Hypertension
- Dysglycemia
- ↑LDL, etc.
Summary and Conclusions

In the stable coronary syndromes:

• Dyshomeostasis, at the coronary microvascular level (e.g. CMD), plays a critically important role in symptoms/signs of ischemia.

• CMD is closely linked to RFs and has prognostic value.

• Recognizing that SIHD does not necessarily require a flow-limiting stenosis in a large coronary artery, and severe stenosis does not necessarily cause all ischemic syndromes, advances our understanding of disease process(es) underlying these syndromes and ultimately will lead to improved diagnostic approaches and therapies.