Microvascular Angina in Women

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No Disclosures
Outline

• Understand gender based differences in ischemic heart disease (IHD)
• Recognize differences in symptomatology
• Review theorized pathophysiological differences and why traditional therapies may be lacking
• Learn focus for future diagnostic and treatment strategies.
Mortality

• Since 1984, more women than men have died annually from ischemic heart disease (IHD), refuting the notion that this is a “man’s disease” and suggesting that it might be relabeled a “woman’s affliction”

(WISE study, JACC 2006, 47:4s-20s)
Cardiovascular Disease Mortality Trends for Males and Females
United States: 1979–2004

Source: NCHS and NHLBI. Note: The overall comparability for CVD between the ICD/9 (1979–98 and ICD/10 (1999–04) is 0.9962. No comparability ratios were applied.

Death rates are age-adjusted per 100,000 population, based on the 2000 U.S. standard. Some data are reported according to ICD/9 codes and some use ICD/10 codes.
Mortality

• A 50% decline in heart related mortality since peak in 1960’s
• Substantially reduced rates of decline noted in lower socioeconomic, racial and female subsets.
• In the year 2000, approximately 60,000 more women than men died from cardiovascular disease

(WISE study, JACC 2006, 47:4s-20s)
Delay in treatment

- Atypical nature of symptoms
- Decreased perception of self risk
- **Delayed time to presentation for medical care**
- Delayed recognition
- Less likely to receive appropriate medications at discharge
• In 2001 AHA introduced the “Go Red for Women” campaign to increase awareness
In 2002, National Heart, Lung and Blood Institute initiated the "Heart Truth" program.

Focus of these educational programs was to increase awareness of cardiovascular disease in women age 40 to 60.
CRUSADE

- Increasing awareness = decrease in time to presentation for medical care
  - Women having an MI often delay seeking care compared with men.

Am Heart J 2010;160:80-87.e3
• This study found no reduction in time from symptom onset to hospital presentation for MI since the national awareness campaigns were started.
Gender Differences

• Despite being the leading killer of women at all ages
• Prevalence of obstructive CAD in women is lower than men
• Only begins to approach equivalent prevalence rates in 7th decade of life

(WISE study, JACC 2006, 47:4s-20s)
Gender Differences

• Women more frequently are evaluated and hospitalized for chest pain symptoms

• Chest pain symptoms is less accurate predictor of obstructive CAD in women
Gender Differences

- Each year, 60,000 to 150,000 American women are diagnosed with acute coronary syndrome (ACS) and have no angiographic obstructive CAD.

Am Heart J 2009;158:688-94
Gender Differences

• Female sex is the strongest factor associated with the absence of obstructive CAD in NSTEMI

• One in four women who meet strict criteria for angina at rest, ECG changes or previous documented disease had no obstructive CAD on angiogram.

Gender Differences

• In ACS and non-obstructive CAD on angiography women have 2% risk death or MI within 30 days to 1 year

• 2 yr f/u almost 10% of women with minimal angiographic disease died or had MI

(WISE study, Sharaf et al)
Gender Differences

• **Treatment** for women with non-obstructive coronary artery disease is often
  – Reassurance
  – Sedatives/hypnotics

• Evidence based guidelines for anti-anginal and anti-atherosclerotic agents are often not prescribed
Gender Differences

• The **one year death rate** and rate of reinfarction is **higher in women** than men

• **40%** risk of **rehospitalization** for chest pain

• **30%** rate of repeat **coronary angiography** in 1-5 yrs.

Am Heart J 2009;158:688-94
Gender Differences

- Lower prevalence of obstructive CAD across all age groups
- More adverse outcomes despite lower angiographic disease burden.

• Women are less likely to benefit from clinical risk reduction algorithms focusing on obstructive CAD and coronary revascularization strategies
Gender Differences

• Greater symptom burden
  – Increased health care resource utilization and rate of readmissions
  – Higher rate of functional disability, depression
  – Greater impact on quality of life
Gender Difference Summary

• Paradoxical difference where women have
  – More symptoms, ischemia and adverse outcomes
  – Lower rates of anatomical CAD, preserved LV systolic function

• Rename **CAD** → **Ischemic Heart Disease (IHD)**
SYMPTOMS
Symptomatology

- In approximately 60% of cases, the initial presentation of IHD in women is acute MI or sudden cardiac death.
Symptomatology

• The most common symptom in acute MI is chest pain in both men and women

• But up to 50% of women presenting with acute MI report no chest pain symptoms
Symptomatology

• Chest pain symptoms reported are infrequently “exertional”

• Fatigue, sleep disturbance, SOB, nausea, jaw/arm pain

• “flu-like illness” but without the fever
NO... NO...
I SAID I'VE GOT
ACUTE ANGINA
MICROVASCULAR ANGINA

• Clinical presentation
  – Identify stable vs. unstable symptoms
• Proposed pathophysiology
• Management
September 23, 2008

Tony Braxton in Dancing with the Stars, developed chest pain
Microvascular angina

- Chest pain syndrome in the absence of significant obstructive CAD on angiography
- Microvascular angina has no accurate diagnostic test
- Diagnosis of exclusion
Prinzmetal’s Angina

• Differentiated from Prinzmetal’s angina
  – Epicardial coronary artery vasospasm
  – ECG shows ST segment elevation
  – Stimulated during angiography
    • Ergovine, acetycholine
Prinzmetal’s Angina
Microvascular Angina

• Remains poorly understood:
  – Unlike epicardial disease, small vessel disease cannot be visualized by angiography
  – Complex and time consuming methods would be required to carefully assess coronary microcirculation
  – Accepted hallmarks of ischemia such as stress induced LV dysfunction may be undetectable
Microvascular Angina

• Coronary blood flow (CBF) abnormalities and myocardial alterations in MVA may differ substantially from flow-limiting stenosis in larger coronary arteries
Microvascular Angina

- Sparse distribution of myocardial ischemia, may produce ECG changes and perfusion scintigraphic defects (nuclear stress), but may be insufficient to result in obvious contractile abnormalities
Cardiac syndrome X

- Chest pain symptoms - atypical, prolonged, exertional
- May or may not have evidence of ischemia on ECG, stress testing
- Historically considered a benign prognosis
Cardiac Syndrome X

• Most of proposed models suggest abnormal coronary microvascular resistance
  – These models suggest stable MVA has an exertional component

• Many women have atypical symptoms
  – Rest pain and prolonged symptoms
Cardiac Syndrome Y

• “Coronary slow-flow phenomenon”
  – Resting coronary artery resistances are abnormally elevated
  – Result in resting angina symptoms
  – Seen on angiography as slow opacification of coronary vessel with dye.
  – May not have as benign a prognosis.
Stable vs Unstable

• Increasing frequency, intensity and duration

• Documented ischemic changes on diagnostic testing ie) ECG, stress testing

• Abnormal cardiac enzymes
Stable vs. Unstable

• Stable chest pain symptoms, women have superior survival rate than men.

• Acute coronary syndrome and unstable angina women have higher mortality rates.
Angina normal coronary arteries

Chronic/stable angina syndrome
- Effort angina
- Mixed angina

Vasospastic angina

Stable MVA

Acute/unstable angina syndrome
- Rest angina
- Single episode
- Recurrent episodes
- Crescendo angina

Vasospastic angina
Thromboembolism

Acute/unstable MVA
ANGINA, I’VE ALREADY HAD THAT. CAN’T I HAVE SOMETHING ELSE?
60% of the time initial presentation of IHD in women is **sudden cardiac death** or MI.

- In **Sudden cardiac death**
  - Plaque rupture vs. Plaque erosion
Plaque rupture

- SCD - morphologic differences in etiology
  - Plaque rupture occurs with large necrotic core and disrupted fibrous cap infiltrated by macrophages and lymphocytes
  - Occurs more frequently in men and older women.
Plaque erosion

- SCD- morphologic differences in etiology
  - Fibrous cap is absent at the plaque erosion site and exposed intima consists predominantly of smooth muscle and proteoglycans

JACC 2006;47:21s-9s
Pathophysiology

- Smaller artery size
- Positive remodeling limiting encroachment of plaque into lumen
  - Appearance of “normal coronaries”
- Abnormal smooth muscle reactivity
- Increased inflammatory markers
- Abnormal cardiac pain perception
- Plaque erosion and distal embolization rather than plaque rupture
Pathophysiology

- Proposed factors
  - Abnormal vasoreactivity
  - Higher prevalence of vascular disorders i.e. migraine, Raynaud’s
  - Increased inflammatory markers i.e. CRP
  - Estrogen deficient state i.e. PCOS
  - Higher prevalence of diabetes, HTN
Model of Microvascular Angina in Women

Hormonal Alterations coupled with:

Sex-specific precursors
- PCOS
- Hypoestrogenemia
- Menopause

Pro-atherogenic factors
- Hyperlipidemia, HTN, smoking, metabolic dysfunction, inflammation

Pro-vasculopathy

Microvascular dysfunction

Nonobstructive atheroma

Subendocardial or epicardial ischemia

Accelerating factors
- Early menopause, risk factor clustering

Vascular dysfunction symptoms
- Atypical symptoms, including prolonged symptoms at rest, shortness of breath, unusual fatigue, and more frequent pattern

Evidence of microvascular dysfunction

- Disruption of ovulatory cycling/irregular menses, estrogen deficiency and hypothalamic dysfunction in premenopausal women is associated with increased adverse CVD events – ie) PCOS (polycystic ovarian syndrome)

JACC 2009;54:1561-75
Evidence of microvascular dysfunction

- “Endothelial dysfunction”
- Chronic hyperglycemia results in impaired endothelium dependent and independent coronary vasodilator function
- Brachial artery flow mediated dilatation is impaired in hyperlipidemic, hypertensive, smoking and diabetic women

JACC 2009;54: 1561-75
Evidence of microvascular dysfunction

- Microvascular dysfunction
  - Retinal arterial narrowing, a measure of microvascular disease, is related to CVD events in women but not men

JACC 2009;54: 1561-75
Evidence of microvascular dysfunction

- Non-Endothelial component
  - Altered smooth muscle reactivity
  - Limited coronary microvascular response (decreased coronary flow reserve) to adenosine, predicts adverse outcomes in women.
Pathophysiology

Estradiol

- post-menopause
- hypoestrogenemia
- PCOS
- visceral obesity

Inflammatory milieu

Autoimmune diseases

Hypertension

Obesity

Hyperlipidemia

Abnormal coronary reactivity
- microvascular dysfunction
- endothelial dysfunction
- metabolic changes, decreased perfusion

Positive coronary remodeling
- increased wall thickness, plaque erosion, distal embolization

Normal artery & vascular function

Normal artery & abnormal microvascular vascular function

Subclinical atherosclerosis

Obstructive CAD

Progressive manifestations of ischemic heart disease

Pre-clinical

Clinical

Shaw, L. J. et al. J Am Coll Cardiol
2009;54:1561-1575
Progression of ischemic heart disease in women
Cascade of Mechanisms and Manifestations of Ischemia Having an Impact on Ischemic Heart Disease Risk in Women

- Systolic dysfunction
- Regional wall motion
- Decreased segmental perfusion
- Diastolic dysfunction
- Micro-infarction/myocardial fibrosis
- Altered metabolism/abnormal ST segment
- Decreased subendocardial perfusion
- Endothelial and microvascular dysfunction

Progression of ischemic heart disease

• Obstructive vs. non-obstructive disease
  – Different pathophysiologic mechanisms?
  – Progression of same disease over time?
Evaluation

• Lonstanding management approach to ischemic heart disease has been finding the “culprit vessel”

• A shift towards “culprit patient” or identifying prognostic risk vs obstructive vessel may be more helpful in women and minimize the role of disease-based terminology ie) “false positive” test
Evaluation

• Evidence of smaller arterial size, positive remodeling, microvascular disease on such studies as CIMT, retinal artery assessment, or coronary calcification carry greater prognostic weight in women than men
Evaluation

- Coronary microvascular function can be investigated in cath lab using intracoronary doppler
  - Complete evaluation is complex and time consuming
  - Presents unjustified risks
Evaluation

- Transthoracic echocardiographic doppler recording of coronary blood flow (CBF)
  - Ratio between diastolic CBF velocity at peak vasodilation and CBF at rest
  - Limited to assessment to LAD due to decreased visualization of other vessels by echo.
Evaluation

• Cardiovascular magnetic resonance imaging (CMR) with pharmacological stress test
  – Reliable in detecting segmental or focal myocardial perfusion defects
  – Reduced global or regional coronary blood flow

Circulation 2010;121:2317-25
Diagnosis

Future direction of testing

• Optimal non-invasive model would measure:
  – Ventricular function
  – Regional flow or perfusion
  – Metabolic requirements
  – Vessel wall abnormalities
  – Markers of inflammation
MVA Management

- Typical anti-anginal medications have mixed results
- May be due to differing mechanisms of pathophysiology
- Therapy is empirical because of limited knowledge of its causes
MVA Management

• Beta Blockers
  – Effective in patients with evidence of increased adrenergic activity ie) High resting heart rate or during low workload exercise

• Exercise training
  – Proven beneficial suggest mechanisms of adrenergic modulation play a role
• Calcium channel blockers and nitrates
  – Aim at relaxing smooth muscle
  – Mixed results
  – Partially effective
MVA Management

- Statins and ACE inhibitors
  - Shown to improve endothelial dysfunction
  - Beneficial effects on coronary microcirculation
MVA Management

• Imipramine
  – May reduce abnormal cardiac pain perception through visceral analgesic effect
  – Anticholinergic and alpha-antagonist effects in both coronary and peripheral circulation
Summary

• Relatively low prevalence of obstructive CAD
• Greater prevalence of ischemia, symptom burden/health care utilization and adverse outcomes
• Traditional risk factors contribute to accelerating risk for ischemic heart disease events
Summary

• Given frequent paradoxical findings of angina, ischemia and without obstructive CAD
  – Terminology changes:
    • CAD $\rightarrow$ ischemic heart disease (IHD)
    • Microvascular angina
Summary

- In biomarker positive women interventional strategies are still proven effective
- Evidence based guideline therapies including ASA, Beta Blocker, Statin and ACEI are underutilized and represent an important area for quality improvement