Non-Obstructive Coronary Artery Disease in Women

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February 16, 2019

EMORY WOMEN'S HEART CENTER

Disclosures

- None

Magnitude of the Problem

- Cardiovascular disease is a leading cause of morbidity and mortality in women, regardless of race or ethnicity.
  - The leading cause of death - ischemic heart disease and stroke
- 2 out of 3 women who have a heart attack never fully recover.
- Among women who survive an attack, 46% are disabled with heart failure within 6 years.

Mosca L et al. *Circulation* 2011;123

Ischemic Heart Disease in Women

- Younger women --
  - Higher mortality after MI than men
  - Lower decline in IHD mortality
  - MI incidence increasing
  - Unexplained by traditional risk factors
  - Less obstructive CAD on angiography --- MINOCA (10-15% of ACS, 1-year prognosis is ~5% for all cause mortality)
- Each year in US:
  - >10,000 MIs in women < 45 years
  - >100,000 MIs in women <65 years

Wilmot et al. Circulation 2015; Izadnegahdar et al., J Women's Health 2014; Beltrame J, Journal of Internal Med 2012; Nedkoff et al., Circ CQO 2011; Vaccarino et al., NEJM 1999; Vaccarino et al, Arch Int Med 2009; Bangalore et al., Am J Med 2012; Rosengren et al., Eur Heart J 2001

Women are NOT little Men

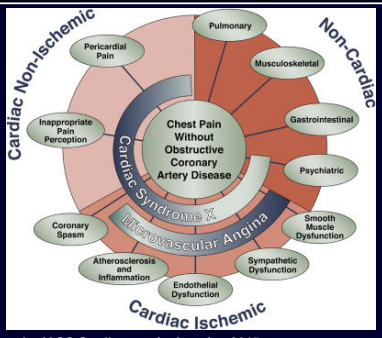
	Women	Men
Spontaneous Coronary Artery Dissection	More	
Diastolic Heart Failure	More	
Pulseless Electrical Activity	More	
Stress/Takotsubo Cardiomyopathy	More	
Myocardial Infarction: Embolic > Plaque Rupture	More	
Risk Factor Differences: Triglycerides Diabetes	Stronger Stronger	
Postural orthostatic tachycardia syndrome (POTS)	More	
Ischemia and No Obstructive CAD – endothelial dysfunction/coronary microvascular dysfunction	More	

	Women	Men
Autoimmune-related CVD	More	
Psychosocial risk factors & CVD: Depression, domestic violence, stress, abuse	More	
Sudden cardiac death		More
Sudden cardiac death with structurally normal heart	More	
Pregnancy-related disorders		
Post-procedural complications	More	
Abnormal Cardiac Nociception	More	
Treatments: Cardiac Rehabilitation, ICD therapy, OMT	Less	
Functional Disability from IHD	More	

IHD Risk Factors in Women

Traditional Risk Factors	Emerging Risk Factors
✓Age	✓Ethnicity
✓Hypertension	Adverse Pregnancy Outcomes
✓Dyslipidemia	Autoimmune diseases
✓Diabetes	Premature Menopause
Obesity	Radiation/Chemotherapy
✓Smoking	Obstructive Sleep Apnea
Family History	Depression
Physical Inactivity	Psychosocial factors
	Environmental

Chest Pain without Obstructive CAD



Marinescu MA et al. *JACC Cardiovascular Imaging 2015.*

Ischemia and No Obstructive Coronary Arteries (INOCA): Major Clinical Problem

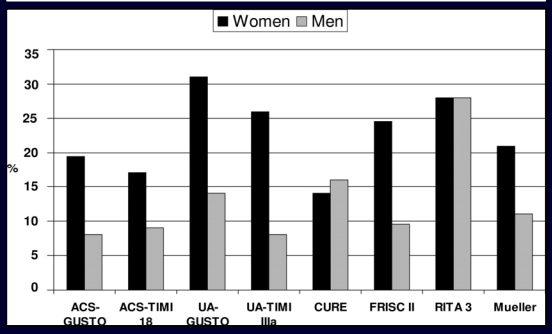
- Patient presents with Angina (typical or atypical)
  - Chest pain/pressure, dyspnea, dizziness, left arm or jaw pain, nausea, weakness, unusual fatigue, etc
- Evidence of myocardial ischemia
  - EKG changes and/or troponin positive
  - Abnormal cardiac stress testing
- Cardiac catheterization - (anatomy)
  - Open arteries
  - No obstructive coronary artery disease (<50% stenosis)

Ischemia and No Obstructive CAD (INOCA)

- ~ 2/3 of women suspected of ischemia have no obstructive CAD on angiography.
- INOCA is not benign - death, MI, stroke, and HF hospitalizations.
- ~ 50% with INOCA have coronary microvascular dysfunction (CMD). ~3 million U.S. women
- No clear clinical practice management guidelines
- High healthcare utilization/costs – repeat cardiac stress testing and repeat angiograms
- Disability, poor satisfaction and quality of life
- Psychosocial risk factors – depression, anxiety

Murthy Circ 2014; Buchthal NEJM 2000; Reis SE et al. *Am Heart J*. 2001;141:735-41.
Von Mering GO et al. *Circulation*. 2004;109:722-725. Bairey Merz et al. Circ 2017;135
Hasdai D et al. *Mayo Clin Proc*. 1998;73:1133-1140. Pepine CJ et al. JACC 2010.

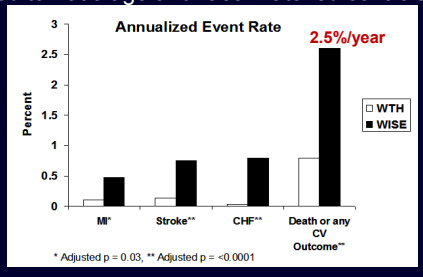
Prevalence of No Obstructive CAD in Acute Coronary Syndrome Studies



Anderson et al. *Circulation* 2007;115:823-826

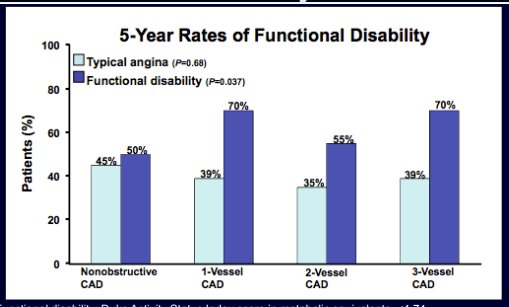
Prognosis of No Obstructive CAD

- N = 540 (WISE)
- Compared to 1000 age and race-matched controls (WTH)



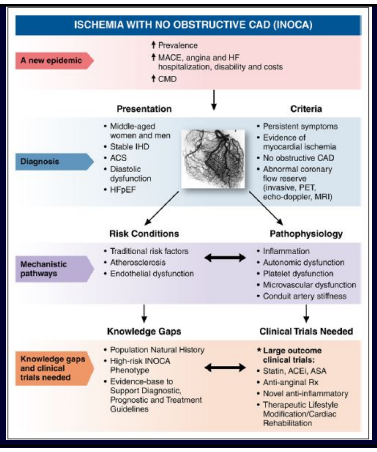
Gulati et al. *Arch Intern Med* 2009;169:843-850

WISE Study: Typical Angina and Functional Disability in Women



Functional disability: Duke Activity Status Index score in metabolic equivalents ≤4.74.
n=883 women presenting for evaluation of chest pain or other equivalent symptoms.
All women had ischemia at noninvasive testing.

Shaw LJ, et al. *Circulation*. 2006;114:894-904.



Bairey Merz et al. Circ 2017

Diagnostic Criteria of MINOCA

1. **Acute MI criteria, including:**
   a. Positive cardiac biomarker: defined as a rise and/or fall in serial levels, with at least 1 value above the 99th percentile upper reference limit.
   b. Clinical evidence of MI, including any of the following:
      i. Ischemic symptoms (chest pain and/or dyspnea)
      ii. Ischemic ECG changes (new ST segment changes or left bundle branch block)
      iii. New pathological Q waves
      iv. New loss of viable myocardium on myocardial perfusion imaging or
      v. New regional wall motion abnormality on left ventricular imaging.

2. **Non-obstructive coronary arteries on angiography**
Defined as the absence of obstructive coronary artery disease on angiography. (ie: no coronary artery stenosis ≥50%, in any potential infarct-related artery). This includes both patients with
   - normal coronary arteries (no stenosis >30%)
   - mild coronary atheromatosis (stenosis >30% but <50%)

3. **No clinically overt-specific cause for the acute presentation**
Defined at the time of angiography, the underlying cause of the clinical presentation and myocardial injury is not apparent

Beltrame JH Sept 2017

What is the Prevalence of MINOCA?

10-15% of Acute MI presentations

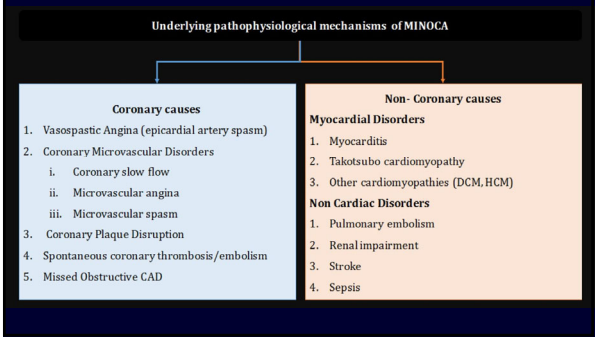
Which Population Predominates in MINOCA?

Women
Younger age

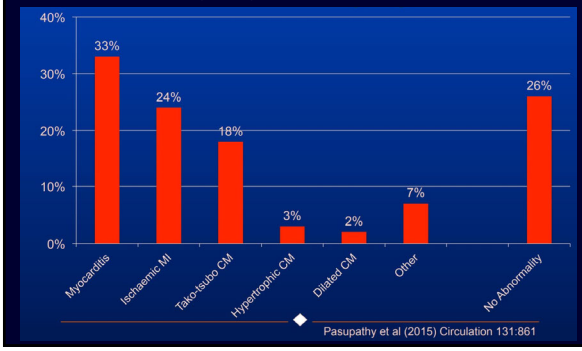
Prognosis of MINOCA

- Current estimates for 1 year after MINOCA
  - 5% of all cause mortality
  - 25% with recurrent angina

Pathophysiologic Mechanisms-MINOCA



Cardiac Magnetic Resonance Imaging in MINOCA



Typical Scenarios

1. Patients who self-refer or are referred by treating cardiologist after unexplained NSTEMI (no obstructive CAD on angiogram)

2. Recurrent rest, emotional stress-induced, or exertional angina

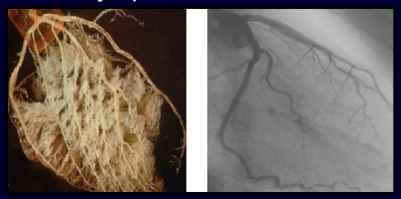
3. Several weeks post- PTCA and have "open" arteries who continue to have angina

4. Younger/peri-menopausal age range (45-55) who have signs and symptoms of ischemia

5. Women with risk factors such as h/o pre-eclampsia, chemotherapy, chest wall radiation, autoimmune disorders (i.e. lupus), migraines or Raynaud's

Coronary Microvascular Dysfunction (CMD)

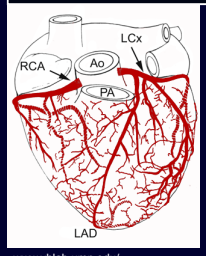
* Term used to describe abnormalities in regulation of myocardial blood flow not explained by epicardial atherosclerosis.



- CMD can be from endothelial dependent or independent mechanisms.

Camici et al. J Nucl Med 2010;50:1076-1087; Recio-Mayoral et a. EHJ 2009; 30: 1837.

Coronary Vascular Resistance

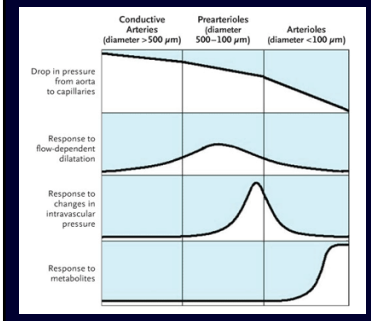


www.vhlab.umn.edu/

- Epicardial arteries normally contribute <10% of the coronary vascular resistance
- Coronary microvasculature is responsible for >70% of the coronary resistance under physiological circumstances.

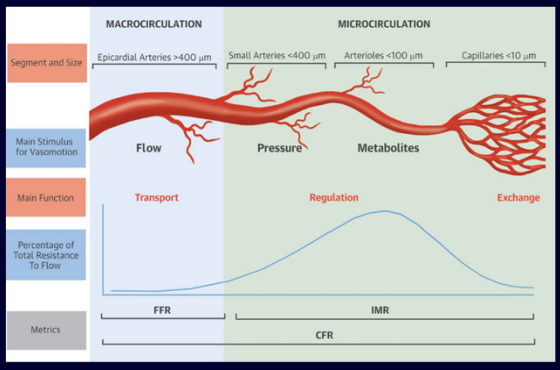
Source: Gould KL et al. *Am J Cardiol.* 1974;33:87–94.
Camici P et al. *Heart, Lung, and Circ.* 2009;18:19-27

Functional Coronary Anatomy



- Epicardial and proximal arterioles – little resistance to flow; maintain a level of shear stress by endothelial-dep vasodilation.
- Pre-arterioles = extramyocardial, and thicker wall than arterioles – myogenic vasoconstriction to maintain flow (sympathetic control)
- Arterioles – high resting tone, dilate to metabolites

Source: Camici PG, and Crea F. *N Engl J Med.* 2007;356:830-40.

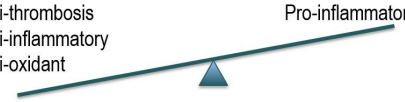


De Bruyne B et al. JACC 2016;67(10)

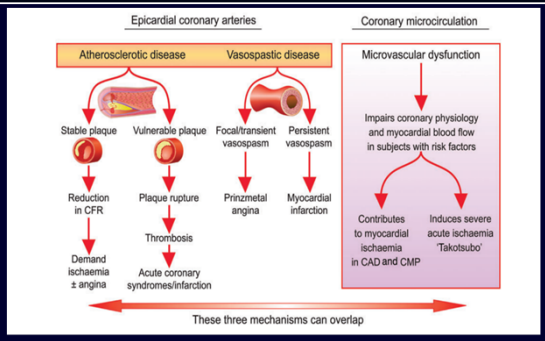
Coronary endothelial dysfunction is a pathological condition

Risk factors and Oxidative stress - Imbalance of factors

Vasodilation Anti-proliferation Anti-thrombosis Anti-inflammatory Anti-oxidant	Vasoconstriction Proliferative Pro-thrombotic Pro-coagulant Pro-inflammatory



Mechanisms of Myocardial Ischemia



Crea et al. *EHJ* 2015

Gender Differences in Ischemic Heart Disease in Women

Structural Features (macro- and micro- vessels)	Functional Features (macro- and micro- vessels)
- Smaller size - Increased stiffness (fibrosis, remodeling, etc) - More diffuse disease - More plaque erosion versus rupture - Microemboli - Capillary rarefaction (drop out)	- Endothelial dysfunction - Smooth muscle dysfunction (Raynaud's, migraine, coronary artery spasm) - Inflammation - Vasculitis (Takayasu's arteritis, rheumatoid, SLE, giant cell, ete)

Wenger NK. *Curr Cardiol Rep.* 2010;12:307:314.
Kramer MC, et al. *J Am Coll Cardiol.* 2010;55:122-132.
Shaw LJ, et al. *J Am Coll Cardiol.* 2009;54:1561-1575.

Pursue non-invasive stress testing for objective evidence of ischemia

- Is patient able to exercise?
- Is baseline EKG ok to pursue ETT (no LVH, LBBB, etc)?
- If yes, start with ETT:
  - Elicit symptoms
  - Detection of Ischemic EKG changes
  - METS and functional capacity
  - Arrhythmias
  - Hypertensive response to exercise

If ETT inconclusive and/or persistent symptoms

- Add an imaging test
  - Stress Echo (diastolic function, hypertrophy, pulmonary hypertension, valvular problems, WMA)
  - Stress PET-CT with Coronary Flow Reserve (added benefit of CAC)
  - Adenosine Stress Cardiac Magnetic Resonance Imaging (added benefit of scar imaging and best for tissue characterization)

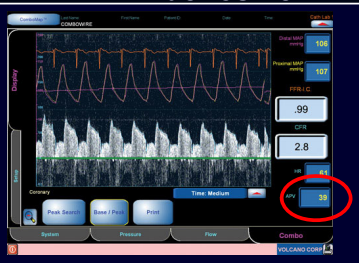
Negative Non-invasive Test Does Not Rule Out Coronary Vasoconstriction

Test	N	% (+)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
Exercise Echocardiogram	99	40.4	38(26–51)	55(38–71)	36(24–49)	58(41–73)
Dobutamine Echocardiogram	21	33.3	29(8–58)	57(18–90)	29(8–58)	57(18–90)
Exercise SPECT	131	38.2	40(29–51)	65(49–78)	38(28–50)	66(51–79)
Vasodilator SPECT	64	50.0	51(35–68)	52(31–72)	41(24–59)	63(44–79)
Vasodilator PET	33	36.4	35(16–57)	60(26–88)	29(11–52)	67(35–90)
All imaging	365	41.4	41(34–47)	57(49–66)	36(30–43)	62(54–70)
Exercise ECG	242	16.1	18(12–25)	80(71–88)	41(33–48)	69(52–83)
All imaging + ECG	365	6.3	6(3–10)	90(83–94)	37(32–43)	61(39–80)

- No vasoconstrictive stimulus for clinical non-invasive testing (such as mental stress, cold pressor, hyperventilation, etc)

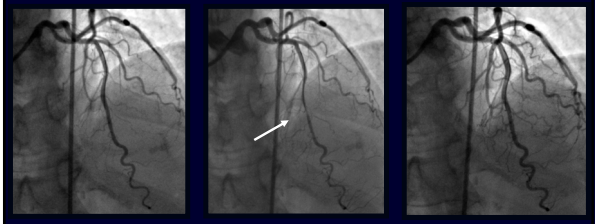
Cassar A et al. Circ Cardiovasc Interv. 2009;2(3): 237–244

Coronary Reactivity Testing: Adenosine



APV= Average Peak Velocity
CBF = Cross section area of coronary artery X APV/2

Macrovascular Coronary Function

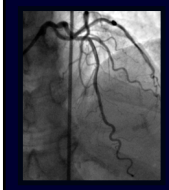


Baseline | Acetylcholine | Nitroglycerin

CRT Safety Data: Out of 293 women, no CRT-related mortality.
0.7% serious adverse events: 1 had dissection, and 1 developed MI from coronary spasm.
MACE Rate at 5.4 year follow up: 8.2%

Source: Wei et al. JACC Interventions 2012;5(6):646

WISE Study Coronary Reactivity Testing Protocol



ADO	18 mcg	18 mcg	36 mcg
ACH	0.364 mcg	36.4 mcg	108 mcg
NTG	200 mcg		

Spasm Testing Dose

**Not done in the setting of ACS
**Higher ACH doses are used in other countries

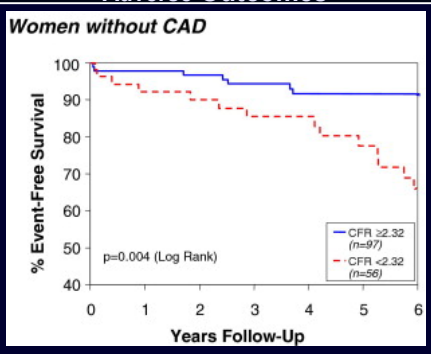
Bairey Merz CN et al. Circulation. 2017;135(11):1075-1092

Components of Coronary Reactivity Testing

	Microvascular Dysfunction	Macrovascular Dysfunction
Non-Endothelial Dependent	CFR <2.5 to Adenosine	Coronary dilation <20% to Nitroglycerin
Endothelial Dependent	ΔCBF <50% to Acetylcholine	Coronary dilation ≤0% to Acetylcholine
Coronary Spasm	Chest pain + ECG changes + significant constriction to Acetylcholine	

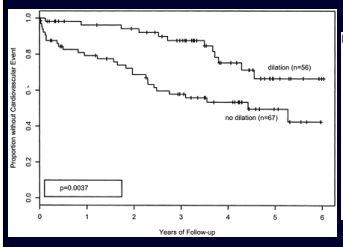
Bairey Merz CN et al. Circulation. 2017;135(11):1075-1092

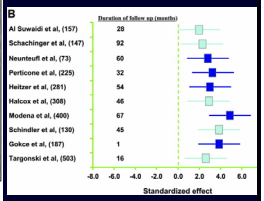
Coronary Flow Reserve to Adenosine Predicts Adverse Outcomes



Source: Pepine CJ et al. JACC 2010.

Endothelial Dysfunction Predicts Cardiovascular Events





Von Mering GO et al. Circulation. 2004;109:722-725
Lerman A, et al. Circulation. 2005;111:363-368

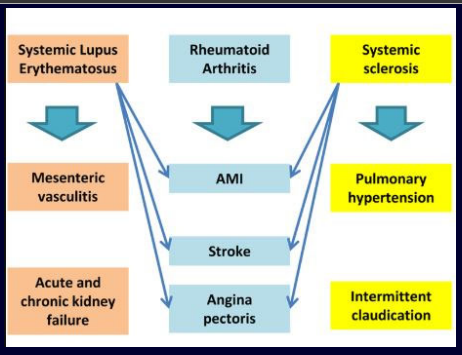
Provocative spasm testing in patients with MINOCA

Publications	No. of Patients in the Study	Provocation Test	Spasm Definition	Provoked/ Spontaneous Spasm, n (%)
Early provocative spasm testing (within 6 wk of acute myocardial infarction)				
Bory, 1988	59	iv ergot	≥50% constriction on angio	2/59 (3%)
Fukai, 1993	21	iv ergot	≥75% constriction on angio	13/16 (81%)
Dacosta, 2001	91	iv ergot	≥70% constriction on angio	11/71 (15%)
Wang, 2002	23	ic ergot	≥90% constriction on angio	17/23 (74%)
Hung, 2003	19	ic ergot	≥70% constriction on angio	18/19 (95%)
Dacosta, 2004	82	iv ergot	≥70% constriction on angio	13/82 (16%)
Abid, 2012	21	iv ergot	≥70% constriction on angio	5/21 (24%)
Ong, 2008	7	ic acetylcholine	≥75% constriction on angio	4/7 (57%)
Legrand, 1982	18	iv ergot	Chest pain & ST elevation	6/18 (33%)
Raymond, 1988	74	iv ergot	≥75% constriction on angio	5/16 (31%)
Ammann, 2000	23	Hyperventilate	ST elevation	0/23 (0%)
Kim, 2005	33	iv ergot	RWMA on echocardiography	20/33 (61%)
Total (provocative spasm testing ≥6 wks)				(31/90) 34%
Undefined timing for provocative spasm testing (relative to myocardial infarction)				
Salem, 1985	10	iv ergot	Chest pain & ST elevation	0/7 (0%)
Verheugt, 1987	21	iv ergot	NR	0/7 (0%)
Provocative spasm testing in cocaine induced MINOCA patients				
*Kosowsky, 1989	5	cold pressor	NR	0%
Overall pooled spasm				114/402 (28%)

*28-34% of MINOCA patients had inducible spasm

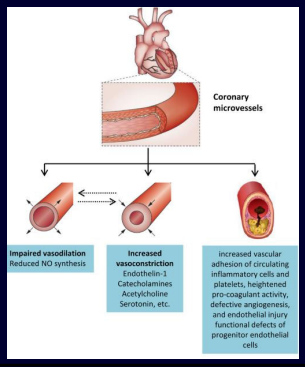
Pasupathy S et al. Circulation. 2015;131:861-870.

Vascular Manifestations – Inflammatory Disorders



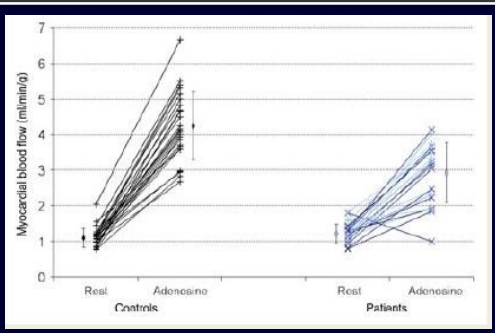
Camici P et al. ESC. Eur Heart J. 2016;37(23):1799-1806. doi:10.1093/eurheartj/ehw018

Mechanisms of CMD that Trigger Events in Inflammatory Conditions



Camici P et al. ESC. Eur Heart J. 2016;37(23):1799-1806. doi:10.1093/eurheartj/ehw018

Myocardial Blood Flow and Chronic Inflammation



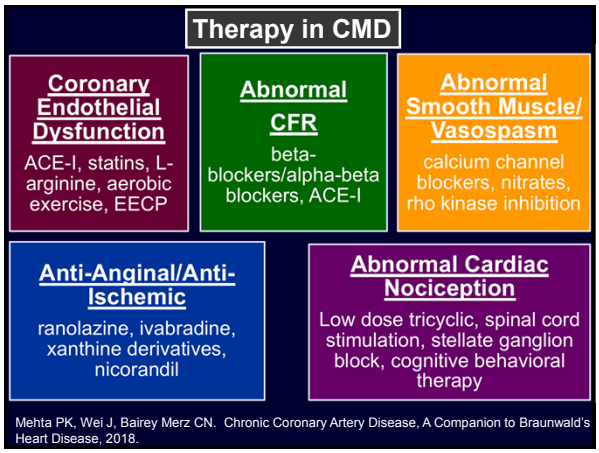
Recio-Mayoral et a. EHJ 2009; 30: 1837.

Pathophysiological mechanism	Clinical investigation	Potential therapy
Coronary plaque disruption		
• Plaque erosion • Plaque rupture	• Optical coherence tomography • Intravascular ultrasound	• Statins
Coronary thromboembolism		
• Thrombosis • Embolism	• Optical coherence tomography • Congenital thrombophilia • Acquired thrombophilia	• Anti-platelet agents • Anticoagulants
Coronary vasomotor dysfunction		
• Coronary artery spasm • Microvascular dysfunction	• Provocative spasm testing • Coronary flow reserve • Microvascular resistance indices	• Calcium channel blockers

Tavella R et al. IJC 2018;267:54-55

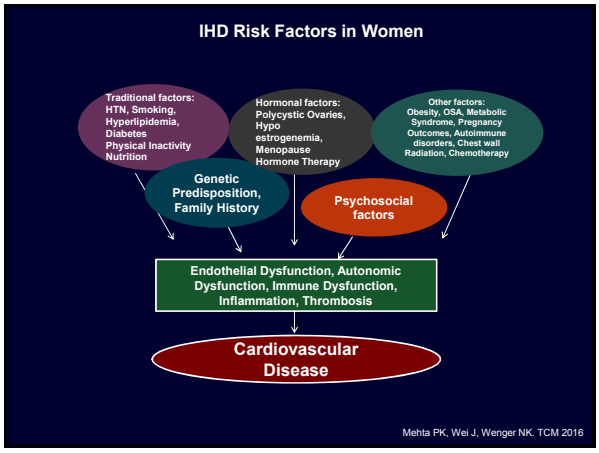
Treatment

- Tobacco cessation
- Cardiac Rehabilitation – Angina/IHD
- Mediterranean diet
- Sleep hygiene/treat sleep apnea
- Treat risk factors – DM, HTN, Hyperlipidemia, etc
- Stress management/depression treatment



Brain-Heart Connection

- Mental stress myocardial ischemia
- Takotsubo Cardiomyopathy

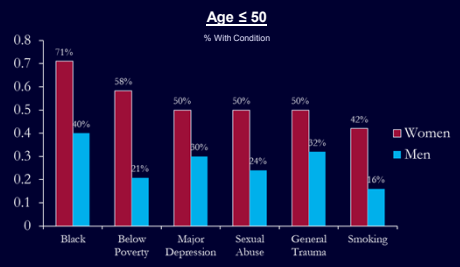


Psychosocial Factors

- Low Socioeconomic Status/Income
- Marital Stress
- Work/Job Stress
- Anxiety
- Depression/hopelessness
- Anger
- Hostility
- Smaller social networks/social isolation
- Caregiver strain
- Early life adversity
- Optimism (protective)

Young Women with Recent MI Have More Psychosocial/Behavioral Risk Factors Than Men

Myocardial Infarction and Mental Stress Study 1 (MIMS1)

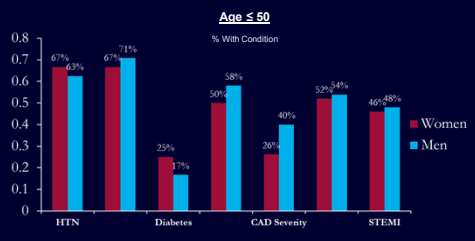


Vaccarino et al. Psychosom Med 2014

Courtesy: Vaccarino

No Difference in Traditional CHD Risk Factors

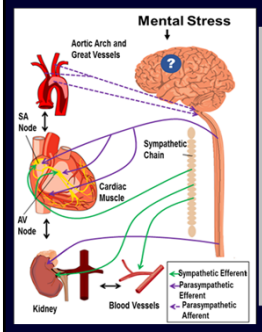
Myocardial Infarction and Mental Stress Study 1 (MIMS1)

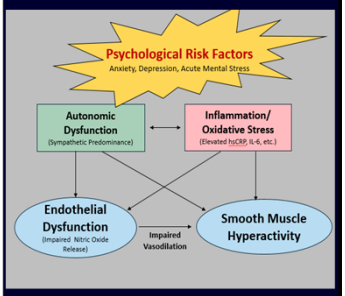


Vaccarino et al., PSM 2014

Courtesy: Vaccarino

Brain-Heart Axis



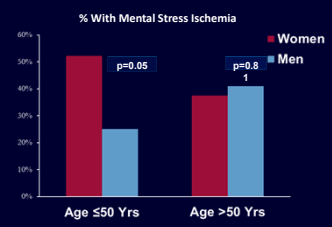


Mehta PK…Vaccarino et al. PSM 2019

Mental Stress Induced Myocardial Ischemia (MSIMI)

- Powerful emotions trigger Angina/MIs
- 3X MACE (independent of cardiac risk factors or presence of exercise-induced ischemia)
- Different mechanism compared to exercise stress– doesn't always accompany physical (exercise/pharm) stress ischemia
- Independent of CAD severity
- Correlates with daily life ischemia
- Marker of susceptibility to emotional stress

Young Women with MI Have More Mental Stress-Induced Myocardial Ischemia



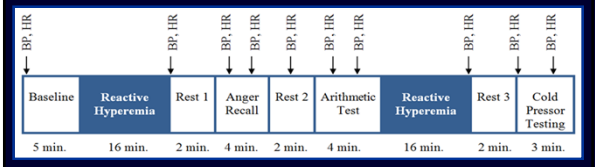
- 98 men and women ≤60 years
- MI in previous 6 months
- SPECT with [99mTc] sestamibi at rest, mental stress, exercise/pharmacologic stress

- No sex differences in exercise-stress ischemia

Vaccarino V et al. Psychosomatic Medicine 2014; 76: 171-180

Cardiac Autonomic Nervous System (CANS) Study: Mental Stress Testing Protocol

- Women with Coronary Vascular Dysfunction (Functional Angiogram)
- Asymptomatic Controls: Age and BMI matched, no risk factors, and normal ETT



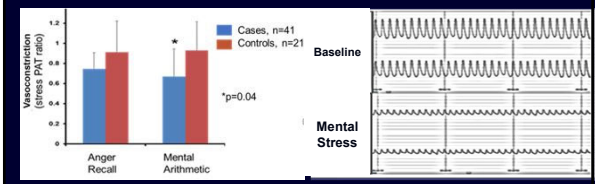
Mehta PK et al. IJC 2017

Hemodynamic Changes to Mental Stress

		Cases Median [min, max] n = 44	Reference Control Subjects Median [min, max] n = 17	p-value
Baseline	HR	67 [47, 90]	61 [50, 83]	0.27
	SBP	115 [90, 165]	116 [94, 145]	0.70
Anger	ΔHR	12 [2, 42]	11 [6, 52]	0.49
	ΔSBP	18 [2, 50]	22 [-4, 54]	0.88
Arithmetic	ΔHR	10 [-1, 53]	17 [-6, 41]	0.08
	ΔSBP	17 [-5, 62]	23 [-6, 39]	0.23
Cold Pressor	ΔHR	1 [-21, 30]	-1 [-14, 17]	0.90
	ΔSBP	19 [-15, 60]	21 [-4, 40]	0.60

Mehta PK et al. IJC 2017

Greater Mental Stress Peripheral Vasoreactivity in Women with Coronary Vascular Dysfunction



Peripheral vasoconstriction inversely correlated with anxiety (r=-3.4, p=0.03), frustration (r=-0.37, p=0.02), & feeling challenged (r=-0.37, p=0.02) in cases but not controls.

Mehta PK et al. IJC 2017

Conclusions

- Ischemia and no obstructive coronary artery disease (INOCA) is highly prevalent and not benign.
- A subgroup of INOCA patients have coronary microvascular dysfunction (CMD), which is associated with adverse CV outcomes.
- Anti-anginal, anti-atherosclerotic, and anti-ischemic therapies, as well as non-pharmacologic approaches can be helpful.
- Large, randomized, therapeutic clinical trials in CMD are lacking, partly due to it's heterogeneous nature, and partly because of lack of diagnostic criteria.

Thank You!

- Emory Clinical Cardiovascular Research Institute (ECCRI)
  - Viola Vaccarino, MD PhD
  - Arshed Quyyumi, MD
- Barbra Streisand Women's Heart Center Clinical and Research Staff
  - C. Noel Bairey Merz, MD
  - Louise Thomson, MD; Daniel Berman, MD
  - WISE Study Team and Investigators
- University of Adelaide: John Beltrame, MD

Grant Support: NHLBI K23HL105787, R01 HL090957 (PI: Bairey Merz)