Sex Differences in Cardiovascular Aging – Cardiovascular Disease, Cognition and Health Policy

Overview: Can Inclusion of Women Improve Men’s Heart Health?

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Average Life Expectancy for North America for those born in 2018 by gender and region (years)

What can we learn about female aging that can improve human health for women and men?
Sex Differences in Cardiovascular Aging Which May Lead to Improved Men’s Health

1) Coronary Microvascular Dysfunction
2) Coronary Arterial Remodeling
3) Left Ventricular Remodeling
Younger women: Plaque erosion:
- Thrombus over a base rich in smooth muscle with proteglycan-rich matrix (necrotic core - often absent): 40% of thrombi in sudden cardiac death

Men and older women: Plaque rupture:
- Thin fibrous cap over large necrotic core Infiltrated by foamy macrophages: 60% of thrombi in sudden cardiac death

Source: Burke Circulation 1998;97:2110-2116.
Morphology of Intramyocardial Emboli in Epicardial Plaque Thrombosis

Women vs. men:
- Any emboli: 73% vs. 37%, p<.001
- Mean emboli: 12 ± 3 vs. 4 ± 1, p=.02

Acute myocardial necrosis:
- Any emboli: 88% vs. 39%, p<.001
- Mean emboli: 18 ± 5, 4 ± 1, p<.001

Burke and Virmani R et al, *Circ 2001*
INOCA (ischemia with no obstructive CAD): Cardiac MRI demonstrating microvascular coronary dysfunction.
WARrior: Women’s IschemiA TReatment Reduces Events In Non-ObstRuctive CAD Trial

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4,422 subjects with angina, no obstructive CAD randomized to IMT (intensive statin and ACE/ARB) vs UC (usual care primary risk factor management) for reduction of MACE (all-cause death, non-fatal-MI, -stroke, or hospitalization for chest pain or HF) funded by the Congressionally Directed Medical Research Program, Department of Defense, USA (NCT03417388)
37,674 male VA patients – 47% non-obstructive CAD
Sex Differences in Cardiovascular Aging

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Female coronary arteries enlarge when transplanted into males (JACC 2003;41:1539-46)

Figure 1. Percent change in vessel area over time of the proximal segment of the left anterior descending artery in hearts transplanted within the same gender (female to female = open circles; male to male = open squares) and in hearts transplanted across gender (male to female = solid circles; female to male = solid squares). *p < 0.05 compared with baseline. †p < 0.05 compared with percent change in vessel area in all other groups. Data are presented as the mean value ± SEM.
WISE Study: Sex Differences in Heart Attack Plaques

Women erode

Men explode

Burke et al Circ 1998
A schematic of mixed segmental and diffuse narrowings and associated pressure drops along the length of the artery at maximum flow. (A) Predominant, more severe single segmental stenoses with less diffuse narrowing, suitable for angioplasty or bypass surgery. (B) Predominantly diffuse disease or multiple stenoses with less segmental narrowing, not appropriate for angioplasty or bypass surgery. Reprinted with permission from Gould KL. Coronary artery stenosis and reversing atherosclerosis, 2nd ed. London: Arnold Publishing, 1999.
Female BM-MNCs were more beneficial than male cells

Nelson, Zenovich, …Taylor
Circ Res 2007
Exploratory Clinical Study to Evaluate the Potential Bioactivity of CLBS14 in Patients with Coronary Microvascular Dysfunction

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NHLBI-SBIR
RESULTS

Incidence of Myocardial Infarction

46,086 hospitalized predominantly male patients with myocardial infarction over 18,691,131 person-years

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Gender differences in pressure overload

Normal

Concentric hypertrophy

Women?!

Men

Pressure load
Hypertension
Aortic stenosis

Adaptive remodeling
thick walls, small ventricle
better reversibility?

Maladaptive remodeling
thin walls, dilatation!
WISE-CVD Continuation (HFpEF) R01 – PI CN Bairey Merz MD - Proposed cascade of events in coronary microvascular dysfunction-related MINOCA, INOCA, and HFpEF

Genetic and Environmental Factors

Arteriolar Remodelling

Microvascular Dysfunction

MINOCA
HFpEF
Arrhythmias
Sudden Death

Myocardial Fibrosis and Scar

LV Remodeling
Diastolic and Systolic Dysfunction

Myocardial Ischemia

Crea, Camici, Bairey Merz EHJ 12/13
Distribution of EF Among Men and Women With HF: 21% and 27% are HFpEF, respectively

Sex Differences in Cardiovascular Aging

1) Vascular Factors in Cognition: The Impact of Sex on Memory – Susan Bell, MBBS, MSCI, MACC

2) Cardiovascular Aging, Sex Differences and Eicosonoids – The Fountain of Youth? – Susan Cheng, MD, MPH, MMSc

3) Bridging the Sex Gap in Early Myocardial Infarction Mortality – Why Sex Matters – Nakela Cook, MD, MPH, FACC