Cardiovascular Disease in Women: A Story in Three Chapters

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Public Lecture
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This HRI/CPC Public Lecture is Dedicated to all SCAD Sufferers and their Families
Cardiovascular Disease (CVD) in Women: A Story in Three Chapters

❖ **Prologue**: Sex differences in CVD

❖ **Chapter 1**: Spontaneous coronary artery dissection

❖ **Chapter 2**: Fibromuscular dysplasia (FMD)

❖ **Chapter 3**: Takotsubo cardiomyopathy (broken heart syndrome)

❖ **Epilogue**: Female-specific CVDs
Prologue: Sex differences in CVD

- The typical image of CVD in our community: a man with poor lifestyle habits

- Health issues in women: breast cancer

- Yet: CVD [coronary heart disease (CHD; heart attacks) and stroke] is the biggest killer of women across the world, and in our society CHD kills 3 times more women than breast cancer
Sex differences in CVD

**Historically:** CVD seen as a disease of men

Figure 1. Mortality rates for coronary heart disease in the USA in 2000, by sex; Global Burden of Disease study data.
Sex differences in CVD

**However:** Women with CHD have a relatively worse outcome than men.
Sex differences in CVD

However: Women with CHD have a relatively worse outcome than men
Sex differences in CVD

**However:** Women with CHD have a worse outcome than men

![Death within 1 year graph]

Woodward Int J Environ Res & Pub Health 2019
Sex differences in CVD

Traditional risk factors (men and women)
Age, smoking, cholesterol, diabetes, high blood pressure, family history of CVD

Female-specific risk factors
Early menarche, early menopause, hysterectomy, early age at first birth, history of miscarriage, history of stillbirth, gestational diabetes, pre-eclampsia

The female disadvantage
❖ Women less likely to receive statins for primary and secondary prevention, anticoagulants for atrial fibrillation, percutaneous coronary interventions for CHD, LVADs or heart transplants for advanced heart failure.

❖ Female patients of male cardiologists have worse outcomes, with no such gender differential for female cardiologists

Certain forms of CVD more common in women
Chapter 1: Spontaneous Coronary Artery Dissection

- SCAD is a disease of the coronary arteries that supply blood to the heart. It presents as a heart attack or sudden death. Due to bleed into the wall of a coronary artery leading to the accumulation of blood **intramural haematoma** (IMH). This IMH cause the wall of the artery to bulge inwards into the cavity of the artery, which obstructs blood flow.

- Predominantly affects women (92-98% of cases), who are relatively young (45-52 yr), not overweight and have a low incidence of traditional risk factors

- It is under-diagnosed – as heart attacks not thought of in younger women or a diagnostic angiogram, or troponin level not obtained

- Now recognised to be the cause of 2-4% of all cases of ACS; 24-36% MIs in women <50 yr; commonest cause of an MI associated with pregnancy
Spontaneous Coronary Artery Dissection

- **Normal artery**
  Three layers:
  - Intima (endothelial cells)
  - Media (smooth muscle cells)
  - Adventitia (connective tissue)

- **SCAD Pathology**
  Intimal tear - classical angiographic appearance of two lumens (cavities)
  
  or

  Intramural haematoma (IMH) without an intimal tear – ? due to rupture of the vasa vasorum

  Reduction in blood flow mainly due to IMH rather than clot (thrombus)

  **TYPE 1**
  ~30% of cases

  **TYPE 2/3**
  ~70% cases

Saw et al. JACC 2016
Spontaneous Coronary Artery Dissection

- SCAD Pathology

Hayes et al. Circ 2018
Spontaneous Coronary Artery Dissection

- **Precipitating stressors**
  Increased shear stress due to an increase in pressure in the chest or to a catecholamine surge can trigger SCAD, particularly in patients with an underlying blood vessel problem (arteriopathy).

Such precipitating stressors include: *intense exercise (particularly isometric)*
  *intense Valsalva (retching, vomiting, bowel movement, coughing)*
  *vasoconstrictor drugs e.g., those used to treat migraine pregnancy (parturition)*
  *bereavement or other major stress*
  *drug abuse (mainly cocaine), high-dose hormonal therapy (e.g., beta-HCG)*
  *coronary artery spasm*
Spontaneous Coronary Artery Dissection

❖ Presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>95.9%</td>
</tr>
<tr>
<td>Radiation to arm</td>
<td>51.5%</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>23.7%</td>
</tr>
<tr>
<td>Radiation to neck</td>
<td>22.2%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>21.1%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19.6%</td>
</tr>
<tr>
<td>Back pain</td>
<td>13.9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.8%</td>
</tr>
<tr>
<td>VT or VF</td>
<td>7.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>1.5%</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
Spontaneous Coronary Artery Dissection

❖ **Management**

Conservative, not PCI
CABG reserved for those with persistent pain or major complications
Long-term management – blood pressure control; β-blockers

❖ **Outcome**

Favourable; in-hospital mortality <5%, although MACEs in 10 – 30%; spontaneous healing, usually within 35 days; can recur in 20-30% of cases, up to 5 recurrences reported, each involving a different artery/branch

❖ **High burden of linked morbidities**

Non-ischaemic chest pain, insomnia, anxiety, depression and even *post traumatic stress disorder* – contributing factors include the unexpected nature of SCAD, lack of known treatments, and relatively high rate of recurrences (in up to 30% of cases; usually involving a different vessel and causing MI in 20%).
Spontaneous Coronary Artery Dissection

❖ Pathophysiological clues

i) Can occur in association with pregnancy - peripartum when hormones rapidly falling

i) Usually occurs around the time of menopause (45 – 52 yr)

i) Associated with other vasculopathies – migraine, fibromuscular dysplasia (but infrequently with inherited collagen vascular disorders, such as Marfan’s, Ehlers-Danlos etc)

iv) Can occur in association with intense physical or emotional stress (catecholamine surge associated with increased shear stress)

v) Genetic predisposition – familial clustering of cases
Spontaneous Coronary Artery Dissection

❖ Hypothesis

SCAD involves a gene-environment (G x E) interaction - a genetic predisposition enhancing susceptibility of the vessel wall to rupture, together with an environmental cue, e.g., an increase in shear stress, triggering dissection.

Further, SCAD is likely a multigenic disorder impairing either integrity of the intima (endothelial cells and/or basement membrane) – Type 1 SCAD, or media (smooth muscle cells; internal elastic lamina) or adventitia (extracellular matrix, vasa vasorum) – Type 2/3 SCAD

❖ How can we dissect SCAD pathophysiology?
Dissecting SCAD pathophysiology

Cohort: ~280 cases (>97% Caucasians), including 12 familial cases in which more than one family member has had an episode of SCAD. Most accrued as a result of a social media survey (SCAD Support Group – Facebook).

1. Genomic studies
In collaborative studies, we evaluated, found and reported* on the identification of a variant (alternate spelling) in a gene (*PHACTR1*) previously associated with multiple vascular disorders, that is strongly and independently associated with SCAD (OR 1.67; 95% confidence interval 1.50 to 1.86; p = 6.76 x 10e23).

We have now also completed whole genome sequencing on the DNA of ~107 SCAD patients including many of the familial SCAD cases.

* Adlam et al., *J Am Coll Cardiol* 73:58-66, 2019
Spontaneous Coronary Artery Dissection

Dissecting SCAD pathophysiology

2. Generation of induced pluripotent stem cell lines from patients with SCAD

Mishra et al.
Stem Cell Res
2019
Chapter 2: Fibromuscular dysplasia (FMD)

- Like SCAD, FMD is predominantly a disease of women (>90%) with a mean age at diagnosis of 52 yr (5–83), and familial clustering has been reported but is low (~10% of cases).

- Also like SCAD, it is a non-atheromatous, noninflammatory vascular disease.

- FMD manifests as arterial stenosis, tortuosity, aneurysm, or dissection causing high blood pressure or infarction (renal artery), or migraine, TIA, stroke (cervical arteries).

- Two types: **focal** - uncommon; tubular stenosis due to intimal fibroplasia or rarely medial hyperplasia

  **multifocal** - common; alternating stenoses caused by fibromuscular ridges (myofibroblast proliferation) and dilatation, caused by smooth muscle cell/fibroblast/matrix loss, giving classic ‘string of beads’ pattern.
Fibromuscular dysplasia

**Vessels involved**
Renal arteries (80%)
Extracranial carotids (74%)
Less commonly: mesenteric, iliac
?? Coronaries

Olin et al.
Cardiovasc Res
2019
Fibromuscular dysplasia

Pathophysiology

❖ Remains unclear. Overall disorganization of the medial layers is evident histologically with clear loss of smooth muscle cells

❖ High proportion of early-middle age women suggests hormone-associated vascular remodelling, but direct mechanism still missing

❖ Excessive pulsatility of arteries causing micro-traumas has been suggested

❖ Occlusion of vasa vasorum resulting in intimal hyperplasia and myofibroblast transformation of smooth muscle cells
Fibromuscular dysplasia

Canine iliofemoral artery 200 days post occlusion (thrombin-gelatin) (A) or in control (B)

Fibromuscular dysplasia

Myofibroblast (MF) in secretory state typical of fibrodysplasia, after VV occlusion with prominent Golgi complexes (GC), fibrous bundles

Fibromuscular dysplasia

Associations

Extra-coronary FMD is frequently found (45 - 86% cases) in SCAD patients
### Fibromuscular dysplasia

#### Genetics:
Like SCAD is associated with the same *PHACTR1* genomic variant.

<table>
<thead>
<tr>
<th>SCAD</th>
<th>Odds Ratio of Disease if G Allele Present (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Fibromuscular Dysplasia | [Diagram] | Adlam et al.  
Kiando et al. |
| Cervical Artery Dissection | [Diagram] | Debette et al. |
| Migraine Headache | [Diagram] | Freilinger et al. |
| Migraine Headache | [Diagram] | Anttila et al. |
| Coronary Artery Disease | [Diagram] | Nikpay et al. |
| Coronary Artery Stenosis Severity | [Diagram] | Hager et al. |
| Myocardial Infarction | [Diagram] | Beaudoin et al. |
| Myocardial Infarction | [Diagram] | Nikpay et al. |
| Coronary Artery Calcification | [Diagram] | O’Donnell et al. |

\[ \leftarrow \text{A allele associated with disease} \quad G \text{ allele associated with disease} \rightarrow \]

Fig. 4. Studies indicating disease associations at rs9349379.
Fibromuscular dysplasia (FMD)

Pathophysiology

Olin et al.
Cardiovasc Res
2019
Fibromuscular dysplasia (FMD)

Pathophysiology

ROC Curve

FMD test based on protein and lipid data

<table>
<thead>
<tr>
<th>Predicted Disease Status</th>
<th>True Disease Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FMD</td>
</tr>
<tr>
<td>FMD</td>
<td>18</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
</tr>
</tbody>
</table>

Sensitivity: 78.3%
Specificity: 64.3%
PPV: 64.3%
NPV: 78.3%

Chapter 3: Takotsubo Syndrome (TS)

- Acute heart dysfunction that is transient (<21 days)

Takotsubo = Japanese octopus trap
Chapter 3: Takotsubo Syndrome (TS)

- Like SCAD and FMD, TS is predominantly a disease of women (>90%). However, it is relatively uncommon (1% of ACSs), and occurs more often, almost two decades later in postmenopausal women (mean age ~67 yr).

- Also like SCAD, it is frequently preceded by severe emotional stress (women; usually negative but can be unexpectedly pleasant) or physical stress (men) in the preceding 1-5 days, and presents with an ACS (chest pain, shortness of breathe, dizziness, syncope).

- Like SCAD and FMD it is a non-atheromatous, non-inflammatory vascular disorder, but involves the small (micro) vessels in the heart, rather than the main large coronary arteries.
Takotsubo Syndrome

Coronary artery flow is impaired in Takotsubo cardiomyopathy (TC) and microvascular angina (MVA) vs controls (CG) – reflecting microvascular dysfunction

TFC, TIMI frame count; LAD, left anterior descending, RCA, right coronary artery, LC, left circumflex

n = 27/group

Loffi et al. BioMed Res Int, 2018
Takotsubo Syndrome

Pathophysiology

- Transient coronary artery occlusion
- Coronary artery spasm
- Microvascular dysfunction
- Left ventricular outflow tract obstruction
- Hormonal: oestrogen is vasodilatory and modulates sympathetic tone both at the level of the CNS and peripherally at the level of suppression of $\beta$-ARs. May in part explain why TS most common postmenopausally
- Genetics: vague; a few cases of familial clustering reported; polymorphisms in $\beta$-AR; $G$-protein-coupled receptor kinases (GRK 4/5); Bcl-associated gene 3
- Catecholamine-mediated cardiac toxicity
Takotsubo Syndrome

Pathophysiology

A single injection of an adrenaline-like drug, isoproterenol (ISO), causes widespread heart muscle cell death through Ca^{2+} leakage (RyR2 hyperphosphorylation).

Ellison et al. JBC 2007
Takotsubo Syndrome

**Pathophysiology**

- **Emotional Stress**
  - Negative (and positive) emotions
  - Natural disasters

- **Physical Stress**
  - Trauma/Surgery
  - Medications
  - Intoxication
  - Drug withdrawal

**Risk Factors**

- Female sex
- Post-menopause
- Schizophrenia
- Anxiety/Depression
- Asthma/Chronic obstructive pulmonary disease
- Diabetes
- Chronic medications
- Substance abuse disorders

**Central Nervous System**

- Hypothalamus
- Pituitary

**Neurochemical Mechanisms**

- Catecholamines
- Neuropeptide Y

**Cardiac Dysfunction**

- Direct Cardio-Inhibitory Effects
- Acute Microvascular Dysfunction

**Stress Cardiomyopathy**

Medina de Chazal et al.
JACC 2018
Takotsubo Syndrome

Pathophysiology

Of interest, the emotional stress of a SCAD episode can cause TS, and TS has been postulated to be a cause of SCAD.

However, TS occurs less commonly than SCAD and in women ~2 decades older than SCAD sufferers.
Takotsubo Syndrome

Outcomes

- TS has been considered to be a relatively benign condition. However, more recently complications reported in up to 50% of cases.
- Complications: acute heart failure, cardiogenic shock (often associated with LVOTO), ventricular arrhythmias, stroke due to thrombus formation in LV apex.
- 5-year prognosis similar to that of myocardial infarction.
Epilogue: Female-specific CVDs

- SCAD
- FMD
- Takotsubo

- Stress
- Hormones
- Genetics
## Epilogue: Female-specific CVDs

<table>
<thead>
<tr>
<th>SCAD</th>
<th>F:M ~9:1</th>
<th>Peak age</th>
<th>Presentation</th>
<th>Vessel Involve</th>
<th>Complication</th>
<th>Genetics</th>
<th>Recurrences</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>45-52</td>
<td>ACS</td>
<td>Coron. artery</td>
<td>MI; death</td>
<td>++</td>
<td>Yes (20-30%)</td>
<td>Favourable</td>
</tr>
<tr>
<td>FMD</td>
<td>F:M ~9:1</td>
<td>52</td>
<td>Hypertension</td>
<td>Renal/Carotid</td>
<td>Stroke</td>
<td>++</td>
<td>N/A</td>
<td>V. good</td>
</tr>
<tr>
<td>TS</td>
<td>F:M ~9:1</td>
<td>67</td>
<td>ACS</td>
<td>Coron. microvasculature</td>
<td>Cardiogenic shock; death</td>
<td>?</td>
<td>Yes</td>
<td>Favourable</td>
</tr>
</tbody>
</table>
Cardiovascular Disease (CVD) in Women: A Story in Three Chapters

THANKS

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