Mental Stress-Induced Myocardial Ischemia

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Professor
Psychiatry & Behavioral Sciences
Internal medicine
January 15, 2015
## Disclosure Statement

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tbody>
<tr>
<td>Research Grant</td>
<td>NHLBI and NIMH</td>
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<td>Other Research Support</td>
<td>• Medication / placebo supplement by Forest Laboratory Inc. for REMIT trial</td>
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<td>Speaker’s Bureau/Honoraria</td>
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<td>Expert Witness</td>
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<td>Ownership Interest</td>
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<td>Consultant/Advisory</td>
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<td>Off-Label of medications or Interventions</td>
<td>Escitalopram on mental stress-induced myocardial ischemia</td>
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<td>Other</td>
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Acknowledgement

Jim Blumenthal
Chris O’Connor
Red Williams
Rob Califf
Ranga Krishnan
Joe Rogers
Mike Blazing
Kristin Newby
Eric Velazquez
Zainab Samad
Tom Ortel
Cindy Kuhn
Ralph Corey
Rick Becker
John Alexander
Mike Babyak

Steve Boyle
Jennifer Wilson
Kevin Prybol
Shelby Ladd
Caroline Masterberger
Jeff Copper

Colleagues in the Medicine & Psychiatry program
Duke CDU
Dr. Ortel’s lab
Dr. Kuhn’s lab
Duke Heart Center
DCRI
Depart. Medicine
Depart. Psychiatry
NHLBI
NIMH

Colleagues outside of DUMC
Forest Laboratory Inc.
Pfizer Inc.

My Family
People at Duke Cares!

James Blumenthal, Ph.D.
Co-Director of Mental Health

Duke vs. Wake Forest
Human vs. Monkey

1989

JUNE 4TH PROTESTS
Patients
Outlines

- What and Why is MSIMI
- Evidence based Effective Intervention on Reducing MSIMI
- Underlying Mechanisms Explaining MSIMI
- Future directions
CHALLENGES
The Non-Parallel Rates of Death & Hospitalization due to IHD

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>N</th>
<th>Period</th>
<th>Outcome</th>
<th>PCI</th>
<th>Medical</th>
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<tbody>
<tr>
<td>2003</td>
<td>RITA-2</td>
<td>1008</td>
<td>7-yr</td>
<td>Death or MI</td>
<td>14.5%</td>
<td>12.3%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Re-Vascul</td>
<td>30.2%</td>
<td>35.4%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Re-Vascul/Yr</td>
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<td>3.6%</td>
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<tr>
<td>2004</td>
<td>MASS-II</td>
<td>408</td>
<td>1-yr</td>
<td>Death</td>
<td>4.4%</td>
<td>1.5%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>STEMI</td>
<td>8%</td>
<td>3%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Re-Vascul</td>
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<td>8.3%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Angina</td>
<td>21%</td>
<td>54%</td>
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<tr>
<td>2007</td>
<td>COURAGE</td>
<td>2287</td>
<td>4.6-yr</td>
<td>Death/MI/Stroke</td>
<td>20.0%</td>
<td>19.5%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Admission for ACS</td>
<td>12.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MI</td>
<td>13.2%</td>
<td>12.3%</td>
</tr>
<tr>
<td>2010</td>
<td>?</td>
<td>532</td>
<td>1-yr</td>
<td>Death</td>
<td>13.5%</td>
<td>10.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>486</td>
<td></td>
<td>MI</td>
<td>5.3%</td>
<td>5.6%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Re-Vascul≤1yr</td>
<td>14.7%</td>
<td>6.0%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Angina</td>
<td>38%</td>
<td>49%</td>
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</table>
Optimal Medical Therapy with or without PCI for Stable IHD

COURAGE Trial

Boden et al. NEJM 2007; 356:1503-1516
Advancement of Knowledge

- Removing epicardial coronary stenosis does not consistently and effectively managing IHD and improving CV prognosis

- IHD has a more complex pathophysiological process than it was originally thought; i.e., one element vs. multiple

- A paradigm shift for IHD care has been called on: From focusing on epi-coronary artery stenosis only to focusing on myocardial ischemia

J Am Coll Cardiol. 2012;60:951-956
Obstructive Coronary Atherosclerosis and IHD: An Elusive Link!

In the current pathophysiological model of chronic ischemic heart disease (IHD), myocardial ischemia and exertional angina are caused by obstructive atherosclerotic plaque, and the clinical management of IHD is centered on the identification and removal of the stenosis. Although this approach has been in place for years, several lines of evidence, including poor prognostic impact, suggest that this direct relationship may present an oversimplified view of IHD. Indeed, a large number of studies have found that IHD can occur in the presence or absence of obstructive coronary artery disease and that atherosclerosis is just 1 element in a complex multifactorial pathophysiological process that includes inflammation, microvascular coronary dysfunction, endothelial dysfunction, thrombosis, and angiogenesis. Furthermore, the high recurrence rates underscore the fact that removing stenosis in patients with stable IHD does not address the underlying pathological mechanisms that lead to the progression of nonculprit lesions. The model proposed herein shifts the focus away from obstructive epicardial coronary atherosclerosis and centers it on the microvasculature and myocardial cell where the ischemia is taking place. If the myocardial cell is placed at the center of the model, all the potential pathological inputs can be considered, and strategies that protect the cardiomyocytes from ischemic damage, regardless of the causative mechanism, can be developed.  

(J Am Coll Cardiol 2012;60:951–6) © 2012 by the American College of Cardiology Foundation
Obstructive Coronary Atherosclerosis and IHD: An Elusive Link!
What is Myocardial Ischemia???

NO
Demand == Supply

YES
Demand == Supply

Blocked blood supply

Damaged heart muscle

Occluded coronary artery
Myocardial Ischemia: Nothing Simple at Bedside!

Myocardial ischemia is transient, episodic, with various degree of severity, triggered, and detected via many techniques.

The conventional tests for myocardial ischemia does not fully mimic what the heart experiences in the real life.

How often patients have angina without wall motion defect?
Limitations of Conventional Cardiac Stress Testing

- **Physical stress:**
  - Increase myocardial demand

- **Pharmacological stress:**
  - Increase myocardial demand
  - Dilate non-diseased vessels

- Lack of stress testing that reflects the real life experience and/or process
Adverse Linkage between the Mind and the Heart

- Many studies have documented that several psychosocial factors are chronically associated with development and prognosis of cardiovascular diseases.

- Many studies have also documented that acute events that trigger fear, sadness, or anger, are associated with rapid surge of death and/or major cardiovascular events.
AMI & Death Increase Following Earthquake

Kloner et al. J Am Coll Cardiol. 1998;32:553-4

Missile Launched & MI ↑

Stock Market ↓ & ACS ↑

Daily incidence of acute myocardial infarction in ICCU during Jan 8–25, 1991 (closed columns), compared with same period in 1990 (open columns).


Fiuzat & O’Connor et al. AJC 2010;106:1545-9
Rozanski et al., J Am Coll Cardiol. 2005;45:637-51
Heart Failure Survival over 12-year

Green: BDI<10  
Red: BDI≥10

# Population Attributable Risks for MI – INTERHEART Study

<table>
<thead>
<tr>
<th>Region</th>
<th>HTN %</th>
<th>Diab %</th>
<th>Abd Obs %</th>
<th>PS%*</th>
<th>Lipids %</th>
<th>All 9 RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. Europe</td>
<td>22.0</td>
<td>14.9</td>
<td>63.6</td>
<td>38.9</td>
<td>44.6</td>
<td>94.0</td>
</tr>
<tr>
<td>E/C Europe</td>
<td>24.5</td>
<td>9.1</td>
<td>28.0</td>
<td>4.9</td>
<td>35.0</td>
<td>72.5</td>
</tr>
<tr>
<td>Middle East</td>
<td>9.7</td>
<td>15.5</td>
<td>26.7</td>
<td>41.6</td>
<td>70.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Africa</td>
<td>29.9</td>
<td>17.1</td>
<td>58.3</td>
<td>40.0</td>
<td>74.1</td>
<td>97.4</td>
</tr>
<tr>
<td>S. Asia</td>
<td>19.4</td>
<td>12.1</td>
<td>37.0</td>
<td>15.9</td>
<td>58.7</td>
<td>89.4</td>
</tr>
<tr>
<td>China</td>
<td>22.1</td>
<td>10.0</td>
<td>5.5</td>
<td>35.6</td>
<td>43.8</td>
<td>89.9</td>
</tr>
<tr>
<td>S.E. Asia</td>
<td>38.4</td>
<td>21.0</td>
<td>58.0</td>
<td>26.7</td>
<td>67.7</td>
<td>93.7</td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>22.8</td>
<td>7.2</td>
<td>61.6</td>
<td>28.9</td>
<td>43.4</td>
<td>89.5</td>
</tr>
<tr>
<td>S. America</td>
<td>32.8</td>
<td>12.8</td>
<td>45.4</td>
<td>35.6</td>
<td>47.6</td>
<td>89.4</td>
</tr>
<tr>
<td><strong>N. America</strong></td>
<td>18.9</td>
<td>7.9</td>
<td>59.6</td>
<td>51.4</td>
<td>50.5</td>
<td><strong>98.7</strong></td>
</tr>
<tr>
<td><strong>Overall 1</strong></td>
<td>23.4</td>
<td>12.4</td>
<td>33.7</td>
<td>28.8</td>
<td>53.8</td>
<td>90.4</td>
</tr>
<tr>
<td><strong>Overall 2</strong></td>
<td>17.9</td>
<td>9.9</td>
<td>20.1</td>
<td>32.5</td>
<td>49.2</td>
<td>90.4</td>
</tr>
</tbody>
</table>

*Psychosocial Risks (PS): perceived stress at work or home, financial stress, stressful life events, depression, and perceived disempowerment

## Findings of Clinical Trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>Agents</th>
<th>N</th>
<th>R</th>
<th>Period</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roose &amp; Nelson 1998-99</td>
<td>Nortriptyline vs. Paroxetine</td>
<td>81</td>
<td>y</td>
<td>6w</td>
<td>Depression Drug safety</td>
<td>Both effective TCA toxic</td>
</tr>
<tr>
<td>M-HART 1997</td>
<td>Therapy reduce psychosocial stress</td>
<td>1376</td>
<td>y</td>
<td>?</td>
<td>prognosis</td>
<td>Not effective</td>
</tr>
<tr>
<td>ENRICHED 2001</td>
<td>CBT</td>
<td>2481</td>
<td>y</td>
<td>11 session / 24m</td>
<td>Depression Prognosis</td>
<td>Modest effective Not effective</td>
</tr>
<tr>
<td>SADHART-MI 2002</td>
<td>Sertraline vs. Placebo</td>
<td>369</td>
<td>y</td>
<td>16w</td>
<td>Depression Safety Prognosis</td>
<td>Effective Safe Not definitive</td>
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</table>
# Findings of Clinical Trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>Agents</th>
<th>N</th>
<th>R</th>
<th>Period</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIND-IT 2006</td>
<td>Mirtazapine vs. Placebo</td>
<td>190</td>
<td>y</td>
<td>24w</td>
<td>Depression Prognosis</td>
<td>Not effective Not effective</td>
</tr>
<tr>
<td>CREATE 2007</td>
<td>Citalopram ± IPT</td>
<td>284</td>
<td>y</td>
<td>12w</td>
<td>Depression</td>
<td>Effective Not effective</td>
</tr>
<tr>
<td>SADHART-CHF 2008</td>
<td>Sertraline vs. Placebo</td>
<td>470</td>
<td></td>
<td>12W</td>
<td>Depression Prognosis</td>
<td>Not effective Not effective</td>
</tr>
</tbody>
</table>
Clinical Trial Findings are Perplexed

- Results of several large clinical trials, pharmacological and psycho-behavioral, that primarily aimed at improving depression and/or social isolation, either had no effects on depression reduction, or no benefits on cardiovascular prognosis, or on both, or even detrimental.
Puzzles

- What is(are) missing?
- What is(are) the underlying biomechanism(s) underlying the brain-mind-heart adversity?
- Is there any biomarker that may better guide the investigations on interventions that may modify the brain-mind-heart adversity?
Stress Mechanisms Promoting Atherosclerosis and IHD

Need More Specifics

HPA=Hypothalamic-Pituitary Adrenal Axis, SNS=Sympathetic Nervous System
Who & Why is More Vulnerable?

Two different “phenotypes” for survival

Individuals with personal profile A

Individuals with personal profile B
Psychosocial Factors
## First Report of MSIMI in 1984

### Myocardial Ischemic Activity

<table>
<thead>
<tr>
<th>Test</th>
<th>Subjects (N=16 vs. 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Arithmetic Test: 15 minutes</td>
<td>Angina &amp; Exercise Stress Test +</td>
</tr>
<tr>
<td>Abnormal regional perfusion</td>
<td>75%</td>
</tr>
<tr>
<td>ST-depression</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Deanfield et al. Lancet 1984;92:2102-8
Myocardial Ischemia under Mental and Exercise Stress

Fig 3—Changes in regional myocardial uptake of rubidium-82, and in ECG in relation to chest pain before and after mental arithmetic or exercise.
Patients with Stable IHD & +Physical Stress test < 1yr

<table>
<thead>
<tr>
<th>Ischemic Marker</th>
<th>Mental-Induced (%)</th>
<th>Exercise-Induced (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMA</td>
<td>43 (34.1)</td>
<td>63 (50)</td>
</tr>
<tr>
<td>LVEF $\downarrow \geq 5%$</td>
<td>72 (57.1)</td>
<td>45 (35.7)</td>
</tr>
<tr>
<td>ECG ST change</td>
<td>0</td>
<td>44 (35.8)</td>
</tr>
<tr>
<td>Overall Ischemia</td>
<td>84 (66.7)</td>
<td>86 (68.3)</td>
</tr>
</tbody>
</table>

- WMA = left ventricular segmental wall motion abnormality
- 5 mental tasks

Mental Stress Testing into Cardiovascular Research
“Mental Stress & Health” in PubMed
(Total = 52174 on 5/21/2014)

“Mental Stress & Heart” in PubMed
(Total = 9153 on 5/21/2014)
Review article

Systematic review of mental stress-induced myocardial ischaemia

P.C. Strike*, A. Steptoe

Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK

Revised 5 August 2002; accepted 7 August 2002
Approximately 50 studies have reported occurrence of MSIMI primarily among patients with coronary artery disease, angina, and even “health controls”; MSIMI is common in patients with IHD.

Echocardiography, radionuclide ventriculography with/out perfusion imaging, nuclear VEST, positron emission tomography (PET), and electrocardiogram, etc., have been used to assess MSIMI.

MSIMI is analogous to exercise stress ischemia, except that the stimulus is psychological rather than physical.

Strike et al. 2003 The European Society of Cardiology
### Stable IHD Patients Regardless Recent Physical Stress Test (N=310)

<table>
<thead>
<tr>
<th></th>
<th>MS overall (%)†</th>
<th>EX (%)†</th>
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</thead>
<tbody>
<tr>
<td>WMA %</td>
<td>35.6</td>
<td>20.0</td>
</tr>
<tr>
<td>EF drop ≥8%</td>
<td>20.0</td>
<td>4.9</td>
</tr>
<tr>
<td>EF drop ≥5%</td>
<td>37.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Ischemia ECG</td>
<td>0</td>
<td>17.9</td>
</tr>
<tr>
<td>Overall Ischemia</td>
<td>43.5 (MSIMI)</td>
<td>33.8   (ESIMI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MS1</th>
<th>MS2</th>
<th>MS3</th>
<th>EX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>△WMSI</strong></td>
<td>0.03</td>
<td>0.05</td>
<td>0.06</td>
<td>0.04</td>
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<td></td>
<td>(-0.19, 0, 0.44)</td>
<td>(-0.25, 0, 0.87)</td>
<td>(-0.25, 0, 0.87)</td>
<td>(-1.0, 0, 1.32)</td>
</tr>
<tr>
<td><strong>△LVEF</strong></td>
<td>-0.38</td>
<td>-0.66</td>
<td>-0.64</td>
<td>3.9</td>
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<tr>
<td></td>
<td>(-29.0, 0, 14.0)</td>
<td>(-19.0,-1.0, 19.0)</td>
<td>(-20.0, 0, 13.0)</td>
<td>(-24.0, 4.0, 23.0)</td>
</tr>
</tbody>
</table>

MS: three mental stress tasks; and EX: Bruce protocol exercise stress testing

*△WMSI & △LVEF are differences between resting and during stress presented as Mean (Min, Median, Max)

Jiang et al. JACC 2013
Clinical Significance of MSIMI

- MSIMI is more common in patients with clinically stable IHD
- MSIMI does not have to be associated with the angiographic severity of coronary stenosis
- MSIMI is not analogous to conventional stress induced myocardial ischemia
- MSIMI predicts occurrence of transient myocardial ischemia during routine daily living
- MSIMI predicts poor CV prognosis that are independent of conventional CV risks
Mental Stress Induced $\Delta$LVEF and Event-Free Survival

Every one point of MST induced LVEF reduction is associated with 8% increase of having a CV event over an average of 3.5 years.

## MSIMI and Event-Free Survival – Meta Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MSIMI</th>
<th>No MSIMI</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Jain 1995</td>
<td>10</td>
<td>15</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Jiang 1996</td>
<td>23</td>
<td>84</td>
<td>5</td>
<td>42</td>
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<tr>
<td>Krantz 1999</td>
<td>20</td>
<td>45</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Sheps 2002</td>
<td>6</td>
<td>37</td>
<td>9</td>
<td>145</td>
</tr>
<tr>
<td>Babyak 2010</td>
<td>11</td>
<td>26</td>
<td>21</td>
<td>112</td>
</tr>
</tbody>
</table>

Total (95% CI)  
Total events  70 | 47  
Heterogeneity: Chi² = 0.39, df = 4 (P = 0.98); η² = 0% 
Test for overall effect: Z = 4.60 (P < 0.00001)

REMIT Trial Flow Chart

Patients consented (N = 400)

Patients presented for baseline mental stress testing (N = 335)

Yes MSIMI (N = 132)

Randomized (N = 127)

Placebo (N = 63)
- Dropouts (N = 7)
  - No longer want to participate (2), brain tumor, husband’s health, knee surgery, irregular heartbeat, percutaneous coronary intervention
- Completion (N = 56, 88.9%)

SSRI (N = 64)
- Dropouts (N = 8)
  - No longer want to participate (2), study drug-related side effects (2), MD withdrawal, death, found taking escitalopram at randomization, cluster symptoms indicated significant dehydration
- Completion (N = 56, 87.5%)
No MSIMI at endpoint: Escitalopram 29.7% & Placebo 14.3%; OR = 2.53 (95% CI: 1.04–6.15), P = .04

*One participant was found to have no MSIMI during consensual Echo reading

Jiang et al. JAMA 2013
### Table 3. Outcome Measures After Treatment*

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
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<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Usual Care</td>
<td>Exercise</td>
<td>Stress</td>
<td>Exercise and Stress</td>
<td>Stress Management</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Management</td>
<td>Management Groups</td>
<td>Management vs Exercise</td>
</tr>
<tr>
<td>Cardiac changes during stress, %</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental stress</td>
<td>-.16 (0.46)</td>
<td>-.54 (0.44)</td>
<td>-.34 (0.45)</td>
<td>.03</td>
<td>.75</td>
</tr>
<tr>
<td>Exercise</td>
<td>1.66 (0.92)</td>
<td>0.07 (0.86)</td>
<td>2.50 (0.89)</td>
<td>.51</td>
<td>.06</td>
</tr>
<tr>
<td>Wall motion abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental stress</td>
<td>0.09 (0.03)</td>
<td>0.06 (0.03)</td>
<td>0.06 (0.03)</td>
<td>.52</td>
<td>.98</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.49 (0.25)</td>
<td>0.68 (0.23)</td>
<td>0.13 (0.23)</td>
<td>.74</td>
<td>.002</td>
</tr>
<tr>
<td>Vascular endothelial function, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow-mediated dilatation</td>
<td>4.1 (0.48)</td>
<td>5.6 (0.45)</td>
<td>5.2 (0.47)</td>
<td>.03</td>
<td>.58</td>
</tr>
<tr>
<td>Nitroglycerin-induced dilation</td>
<td>13.8 (0.8)</td>
<td>15.9 (0.8)</td>
<td>15.3 (0.8)</td>
<td>.09</td>
<td>.66</td>
</tr>
<tr>
<td>Cardiac autonomic control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in R-R interval, ms</td>
<td>132.2 (21.5)</td>
<td>131.6 (22.2)</td>
<td>193.7 (19.6)</td>
<td>.99</td>
<td>.04</td>
</tr>
<tr>
<td>Baroreflex sensitivity, mmHg</td>
<td>5.1 (0.9)</td>
<td>7.6 (0.9)</td>
<td>8.2 (0.8)</td>
<td>.63</td>
<td>.02</td>
</tr>
<tr>
<td>Aerobic fitness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treadmill duration, min</td>
<td>7.5 (0.2)</td>
<td>8.7 (0.2)</td>
<td>8.1 (0.2)</td>
<td>.002</td>
<td>.14</td>
</tr>
<tr>
<td>Peak VO₂, mL/kg/min</td>
<td>19.4 (0.5)</td>
<td>21.0 (0.4)</td>
<td>20.3 (0.5)</td>
<td>.02</td>
<td>.19</td>
</tr>
<tr>
<td>Psychosocial outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General distress (General Health Questionnaire)</td>
<td>53.6 (0.9)</td>
<td>56.3 (0.9)</td>
<td>56.8 (0.9)</td>
<td>.02</td>
<td>.72</td>
</tr>
<tr>
<td>Depression (Beck Depression Inventory)</td>
<td>10.1 (0.6)</td>
<td>8.2 (0.6)</td>
<td>8.2 (0.6)</td>
<td>.02</td>
<td>.94</td>
</tr>
<tr>
<td>Hostility (Cook-Medley Hostility Scale)</td>
<td>11.8 (0.5)</td>
<td>10.8 (0.5)</td>
<td>11.3 (0.5)</td>
<td>.23</td>
<td>.47</td>
</tr>
<tr>
<td>Anxiety (Spielberger Trait Anxiety Inventory)</td>
<td>37.0 (0.8)</td>
<td>35.2 (0.8)</td>
<td>36.4 (0.8)</td>
<td>.22</td>
<td>.28</td>
</tr>
</tbody>
</table>

*Values are expressed as fitted mean (SE) and are adjusted for age, sex, prior myocardial infarction, pretreatment resting left ventricular ejection fraction, and pretreatment level of the corresponding outcome variable.

---

Blumenthal et al. JAMA 2005;293:1626-34
RR adjusted, Compared to UC:

SM: 0.26; p = .04

Ex: 0.68; p = .34

MSIMI is an integrated & intermediate biomarker linking the negative Brain-Mind-Heart Interplays

Underlying Mechanisms
### Angiographic Coronary Scores with PSIMI & MSIMI

<table>
<thead>
<tr>
<th></th>
<th>Physical Stress-Induced Myocardial Ischemia</th>
<th>Mental Stress-Induced Myocardial Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Group A (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gensini score, median (IQR)</td>
<td>165</td>
<td>60</td>
</tr>
<tr>
<td>Sullivan stenosis score, median (IQR)</td>
<td>4 (2 to 6)</td>
<td>8 (4 to 11)</td>
</tr>
<tr>
<td>Sullivan extension score, median (IQR)</td>
<td>40 (20 to 60)</td>
<td>58 (40 to 69)</td>
</tr>
<tr>
<td>Group B (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gensini score, median (IQR)</td>
<td>94</td>
<td>65</td>
</tr>
<tr>
<td>Sullivan stenosis score, median (IQR)</td>
<td>14 (4 to 41)</td>
<td>26 (9 to 81)</td>
</tr>
<tr>
<td>Sullivan extension score, median (IQR)</td>
<td>5 (3 to 9)</td>
<td>7 (4 to 10)</td>
</tr>
<tr>
<td>Group A+B (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gensini score, median (IQR)</td>
<td>259</td>
<td>125</td>
</tr>
<tr>
<td>Sullivan stenosis score, median (IQR)</td>
<td>15 (4 to 48)</td>
<td>39 (10 to 84)</td>
</tr>
<tr>
<td>Sullivan extension score, median (IQR)</td>
<td>4 (2 to 7)</td>
<td>7 (4 to 10)</td>
</tr>
</tbody>
</table>

Ramandan & Quyyumi et al. J Am Heart Assoc. 2013;
Coronary Microcirculation – The Neglected Systemic Organ

The tip of the iceberg
Resolution >500 μm

The hidden side of the iceberg
Resolution <500 μm
Coronary Artery Lumen Diameters (mm)

- **Arterioles**: $\phi < 100 \mu m$
  - $<$ 40 $\mu m$ diameter
  - Thick smooth muscle layer
- **Metarterioles**
  - Connect arterioles and capillaries
  - Discontinuous smooth muscle layer
  - Serve as shunts
- **Capillaries**
  - Approx. 10 billion in the body
  - 500-700 $m^2$ surface area
  - $<$ 30 $\mu m$ from any cell to a cap
  - 4-9 $\mu m$ diameter, 1 mm long
  - No smooth muscle, contractile endothelial cells but not clear if functional
- **Venules**
  - Larger than arterioles
  - Weak smooth muscle layer
The sublingual microcirculation

The image represents a tissue area of $0.98 \times 0.73 \text{mm}$. 
## Psychosocial Risks of MSIMI

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 307)</th>
<th>MSIMI No (n = 173)</th>
<th>MSIMI Yes (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>63.81 ± 10.48</td>
<td>63.35 ± 10.33</td>
<td>63.63 ± 10.73</td>
</tr>
<tr>
<td>Race, white</td>
<td>81.29</td>
<td>84.9</td>
<td>77.61</td>
</tr>
<tr>
<td>Female</td>
<td>17.42</td>
<td>13.29</td>
<td>22.39*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.98 ± 4.85</td>
<td>29.31 ± 5.06</td>
<td>28.34 ± 4.31</td>
</tr>
<tr>
<td>Living arrangement, alone</td>
<td>15.81</td>
<td>10.98</td>
<td>21.64*</td>
</tr>
<tr>
<td>Marital status, not married</td>
<td>25.81</td>
<td>19.65</td>
<td>32.84*</td>
</tr>
</tbody>
</table>

Univariate analysis demonstrated that women (OR: 1.88, 95% CI: 1.04-3.42, p=0.04), patients who were not married (OR: 1.99, 95% CI: 1.19-3.36, p=0.009), and patients who lived alone (OR: 2.24, 95% CI: 1.19-4.20, p=0.01) were more likely to exhibit MSIMI.

### Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>Men married</th>
<th>Men not married</th>
<th>Women married</th>
<th>Women not married</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men married</td>
<td>1.00</td>
<td>2.57 (1.33-4.97)</td>
<td>3.18 (1.22-8.32)</td>
<td>1.82 (0.98-4.31)</td>
</tr>
<tr>
<td>Men not live alone</td>
<td>1.00</td>
<td>2.25 (1.02-4.93)</td>
<td>1.78 (0.86-3.68)</td>
<td>2.72 (1.03-7.17)</td>
</tr>
</tbody>
</table>

Δ SBP, Δ DBP and Δ HR between Resting and Stress Testing
$\Delta$ Double Product = $\Delta$ SBP $\times$ $\Delta$ HR
Mental and Exercise Induced Wall Motion Abnormalities

Jiang, et al. JACC 2013
Mental and Exercise Induced LVEF Changes

Jiang, et al. JACC 2013
Diastolic Function & Stressed Induced LVEF Δ

Qi & Jiang et al. AHA 2012
Digital Micro-vascular Response During MST

Peripheral arterial tonometry (PAT) ratio
Ex-Vivo Platelet Aggregation $\Delta$
from Rest to Peak of MST in IHD Patients

Harrison & Jiang et al ACC 2013
Association of Depression with MSIMI & ESIMI

Jiang & Blumenthal et al. AHJ
Myocardial Perfusion Ischemia Severity with Mental Stress

P value for trend = 0.03

Summed Difference Score

Quintiles of BDI-II Total Score

BDI-II ≤ 4 (n=24)
4 ≤ BDI-II ≤ 7 (n=20)
7 ≤ BDI-II ≤ 12 (n=12)
12 ≤ BDI-II ≤ 17 (n=4)
BDI-II > 17 (n=19)

Myocardial Perfusion Ischemia Severity with Physical Stress

P value for trend = 0.63

Summed Difference Score

Quintiles of BDI-II Total Score

BDI-II ≤ 4 (n=24)
4 ≤ BDI-II ≤ 7 (n=20)
7 ≤ BDI-II ≤ 12 (n=12)
12 ≤ BDI-II ≤ 17 (n=4)
BDI-II > 17 (n=19)

It’s the palatability

It’s the portion sizes

It’s the stress

It’s the activity levels

It’s the emotions

It’s the sugar
The speculated mechanisms underlying MSIMI: Negative perception of emotional stress triggers a dysfunctional process that primarily occurs in arteriole and microcirculation of the coronary system, relating to mitochondrial dysfunction.
Mitochondrial: Powerhouse of Human Body

A Neglected Systematic Organelle

- *Mitochondria* are the cellular energy generators that supply virtually all the power of one’s body requires for a healthy life.

- An abundance of published studies underscores the critical importance of the *mitochondria* to overall health, especially as we age.
Mitochondrial Dysfunction (MD)

- Defined as alterations in the mitochondria, such as mitochondrial uncoupling or depolarization, inhibition of the mitochondrial respiratory chain, mitochondrial network fragmentation or nuclear DNA mutations, and mitochondrial accumulation of protein aggregates.

- ATP production capacity is altered in MD that have been observed in several pathological states/diseases, including cancer, obesity, muscle and neurological disorders.

- MD alter the secretion of several metabolites, reactive oxygen species production and several cell-signalling pathways.

- Many metabolites, such as fatty acids and derived compounds, are secreted into the blood stream by cells with MD.
Simply put, MD is an energy production problem and can result in many chronic degenerative orders such as depressive disorders, Alzheimer's, Parkinson’s disease, obesity, diabetes, cardiovascular disease and stroke, as well aging.
Mitochondrial Function in Energy Production

Physiological Consequence of Mitochondrial Dysfunction
- Increased Reactive Oxygen Species
- Reduced GABA Interneuron Activity
- Abnormal Calcium Regulation
- Reduced Synaptic Plasticity
Compared to the HF patients who had never depressed (N=40), HF patients with MDD have:

- Increase in activators of NMDA (N-methyl D-aspartate) receptors
- Increase in dicarboxylic acid (DCA) formation from ω-oxidation of fatty acids which indicates reduction in β–oxidation of fatty acids—Sign of mitochondrial defect
- Decrease in inositol level
- Elevation of phenylalanine

Increase plasma level of branched chain amino acids (BCAA)—a marker of poor CV outcome and T2DM

Figure 1 Regulation of the branched-chain amino acid catabolic pathway. A schematic illustration of major steps and enzyme complexes involved in the BCAA catabolic pathway and targeted organs as well as genetic disorders associated with the specific steps. TCA, tricarboxylic acid cycle (also known as the Krebs cycle).
Types of Fatty Acid Oxidation

**Beta:** Major mechanisms, occurring in Mitochondrial matrix

**Alpha:** Predominately taking place in brain and liver

**Omega:** Minor mechanism but becoming important in conditions of impaired Beta-oxidation

**Peroxisomal:** Mainly for trimming of very long chain fatty acids.
Stress Related

Here are ways in which some key body systems react.

1. **NERVOUS SYSTEM**
   When stressed — physically or psychologically — the body suddenly shifts its energy resources to fighting off the perceived threat. In what is known as the “fight or flight” response, the sympathetic nervous system signals the adrenal glands to release adrenaline and cortisol. These hormones make the heart beat faster, raise blood pressure, change the digestive process and boost glucose levels in the bloodstream. Once the crisis passes, body systems usually return to normal.

2. **MUSCULOSKELETAL SYSTEM**
   Under stress, muscles tense up. The contraction of muscles for extended periods can trigger tension headaches, migraines and various musculoskeletal conditions.

3. **RESPIRATORY SYSTEM**
   Stress can make you breathe harder and cause rapid breathing — or hyperventilation — which can bring on panic attacks in some people.

4. **CARDIOVASCULAR SYSTEM**
   Acute stress — stress that is momentary, such as being stuck in traffic — causes an increase in heart rate and stronger contractions of the heart muscle. Blood vessels that direct blood to the large muscles and to the heart dilate, increasing the amount of blood pumped to these parts of the body. Repeated episodes of acute stress can cause inflammation in the coronary arteries, thought to lead to heart attack.

5. **ENDOCRINE SYSTEM**
   Adrenal glands
   When the body is stressed, the brain sends signals from the hypothalamus, causing the adrenal cortex to produce cortisol and the adrenal medulla to produce epinephrine — sometimes called the “stress hormones.”
   Liver
   When cortisol and epinephrine are released, the liver produces more glucose, a blood sugar that would give the body the energy for “fight or flight” in an emergency.

6. **GASTROINTESTINAL SYSTEM**
   Esophagus
   Stress may prompt you to eat much more or much less than you usually do. If you eat more or different foods or increase your use of tobacco or alcohol, you may experience heartburn, or acid reflux.
   Stomach
   Your stomach can react with “butterflies” or even nausea or pain. You may vomit if the stress is severe enough.
   Bowels
   Stress can affect digestion and which nutrients your intestines absorb. It can also affect how quickly food moves through your body. You may find that you have either diarrhea or constipation.

7. **REPRODUCTIVE SYSTEM**
   In men, excess amounts of cortisol, produced under stress, can affect the normal functioning of the reproductive system. Chronic stress can impair testosterone and sperm production and cause impotence.
   In women stress can cause absent or irregular menstrual cycles or more painful periods. It can also reduce sexual desire.
It's the Microcirculation & the Mitochondrial
The "solar system" of IHD

Psycho-Social-Environmental Risks

Microcirculation-Mitochondrial Dysfunction

MSIMI
Metabolomics Profiling on MSIMI and SSRI Intervention

NHLBI R01 Study
Summary

- Technologic advancement has allowed us to better identify the bio-pathological process of the adverse interplay in the brain-mind-CV circuit.
- Mental stress testing provides unique opportunities to evaluate bio-pathological changes that may not be uncovered when the mind-body is still.
- MSIMI is more a later or end biomarker representing the adverse process. Looking for earlier and more sensitive biomarkers of the process is imperative for developing effective intervention and prevention.
Summary

- Many non-cardiac somatic complaints and prevalent mental illnesses are now shown to have MDs and MSIMI is most likely due or related to MD as well.
- The precise mechanisms by which deficits of energy metabolism occur in the brain and particular body part of these patients affected are not completely known. It remains to be determined whether these alterations in mitochondria contribute to the disease process or are just epiphenomena.
Summary

- SSRI, aerobic exercise, and stress management have beneficial effects on MSIMI and CV outcome of patients with IHD.

- Successfully implement these effective intervention to routine clinical practice remains a big challenge
Thank You!

&

Comments?
Tryptophan Metabolites Differ between Patients with / without MSIMI at Rest

Pre-Stress Metabolite Differences In Patients With and Without MSIMI

Key
- Patients without Ischemia
- Patients with Ischemia

All units are measured in pg/mL

N-Acetylserotonin

3-Hydroxykynurenine
Metabolomics Findings between MSIMI Yes & No

A REMIT Pilot

Kynurenine

Uric Acid

N-acetylserotonin

Tyrosine

Methionine