Managing Triad 2 and Triad 3 Relationships
The Role of Endotoxemia and Cardiovascular Health
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The following potential conflict of interest relationships are germane to my presentation.

Equipment: None
Speakers Bureau: None
Stock Shareholder: None
Grant/Research Support: None
Consultant: None
Other: Integrative Health Resources

Status of FDA devices used for the material being presented
NA/Non-Clinical

Status of off-label use of devices, drugs or other materials that constitute the subject of this presentation
NA/Non-Clinical
Triad 2 and 3: Gut, Heart and Vascular Connection
Andrew Heyman, MD MHSA
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Gut-Immune-Brain

- Primary command and control
- Filtering, Defense and Repair
- Major physiologic interfaces
- Normal: Organized and secure
- Imbalanced: Disordered and unpredictable
Brain
• Cognition and memory
• Mood and emotions
• Central control of physiology

Gut
• Single epithelial layer
• Initial metabolism and transformation of biochemicals
• Structural defense

Immune
• Innate and acquired immunity
• Repair cycle
• Cell to cell communication
Intestinal Barrier Physiology

- Intestinal epithelium - largest mucosal surface of body
- Interface between external world and host
- Key functions - Intestinal permeability and mucosal defense
Mucosal Linings of Intestines

- Provides layer of protection to endothelial cells
- Made of glycoproteins – mucin
- Mucin production is upregulated by probiotics
- Can be compromised by stress, drug use, diet, environmental chemicals, gut flora balance, genetic predisposition.
Immunity in the Gut

• Lymphocytes - activity in the microvilli, should be low. If elevated, indicates gluten intolerance/celiac’s and/or food intolerance.

• Inhaled allergens - trigger T-cell response in gut. If friendly flora are depleted, this response is heightened.

• TH-2 activation is seen in autoimmunity
Immunity in the Gut

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- Inhaled allergens - trigger T-cell response in gut. If friendly flora are depleted, this response is heightened.
- TH-2 activation is seen in autoimmunity
Dendritic Cells

- Activate Toll-Like Receptors (9 TLRs)
- Changes phenotype and function of dendritic cells
- TLRs discriminate between self antigens and nonself-antigens
- Different TLR’s in the gut respond to specific stimuli
- TLR’s direct signaling of cytokines and chemokines
- Friendly flora induce TLR4 and reduce food antigens action TLR2 is enhanced and improves gut barrier permeability
Gut-Immune-Brain Pathology

Brain
- Depression and anxiety
- Interrupted sleep
- Persistent fatigue and brain fog

Gut
- Bloating, gas, and stomach pain

Immune
- Known auto-immune disease
- Impaired immunity
Resting Heart Rate

• Remarkably strong association between heart rate and survival, an association that transcends species.
• Small mammals that have rapid heart rates have short life expectancies.
• Larger mammals that have slower heart rates have correspondingly higher life expectancies.
• Among nearly all mammals, life expectancy is close to 1 billion heartbeats.
• Investigators have been able to increase survival in animal models by deliberate slowing of heart rate.
How Fast You Beat……

….Not so Good

Table 2 Resting heart rate by quintile as a predictor of coronary events and stroke in univariable analysis

<table>
<thead>
<tr>
<th>Myocardial infarction or coronary death</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 bpm (referent)</td>
<td>1.00</td>
</tr>
<tr>
<td>63-66 bpm</td>
<td>1.07 (0.94 to 1.23)</td>
</tr>
<tr>
<td>67-70 bpm</td>
<td>1.19 (1.04 to 1.36)</td>
</tr>
<tr>
<td>71-76 bpm</td>
<td>1.21 (1.06 to 1.38)</td>
</tr>
<tr>
<td>&gt;76 bpm</td>
<td>1.68 (1.49 to 1.89)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

bpm=beats per minute. Values are hazard ratio (95% CI) unless otherwise indicated. Stratified for participation in hormone trial, dietary modification trial, and observational study.
LPS and Inflammation

- LPS  Lipopolysaccharide
- LPS make up 75% of the material of the outer cell wall of gram negative bacteria
- 1 single cell death releases 1 million LPS molecules
- Toll receptor known as TLR-4 is stimulated by LPS

What the Heck is a Lipopolysaccharide

- Contains long carbohydrate molecules and fatty acids
- LPS, aka Endotoxin, is structural part of bacteria serves as a barrier to exotoxins from other organisms
- Intestines and Liver remove.
- Stress and shock increases absorption of endotoxin.
- Triggers release serotonin from platelets and causes vasoconstriction
- Serotonin impairs mitochondrial energy production
Endurance & Endotoxin

• Long Duration Exercise induces Endotoxemia due to plasma ↑ Lipopolysaccharide (LPS) levels
• LPS leads to: ↑ cytokine release ↑ oxidative stress and alterations in gut function
• Vitamin C reduced nitrate and LPS serum levels

Endurance and Gut

• 93% of athletes in this study had GI complaints
• 2 abandoned the race due to severe GI distress
• Endotoxemia-dizziness nausea and vomiting mimic heat effects
  • Relationship between gastro-intestinal complaints and endotoxemia, cytokine release and the acute phase reaction during and after a long distance triathlon in highly trained men. Clinical Science (2000) 98, 47–55 (Printed in Great Britain)
Probiotics: Lactobacillus Plantarum genomic DNA

- Inhibits signal pathways of LPS:
  • TNFα
  • TLR4
  • TLR9
- Enhanced
  • IL-1 associated m Kinase

Probiotics have an anti-inflammatory effect

Chung Hee Kim¹, Han Geun Kim², Joo Yun Kim¹, Na Ra Kim¹, Bong Jun Jung¹, Ji Hye Jeong¹, Dae Kyun Chung¹,³,⁴: Probiotic genome DNA reduces the production of pro-inflammatory cytokine tumor necrosis factor-alpha Volume 328, Issue 1, Pages 1–89
Endotoxin LPS Facts

- Has anti-thyroid effects
- Causes blood estrogen levels to rise increases clotting risk
- Intense exercise and fasting increase lactic acid and ammonia production \( \uparrow \) LPS
- Carrageenan in drinks trigger endotoxin
- Associated with auto immunity
LPS and TLR-4

- TLR-4 part of built in pattern recognition to mobilize defenses against pathogens
- Small amounts of LPS trigger innate immunity via TLR-4
- Activates monocytes and macrophages, neutrophils & endothelial cells
- TLR-4 receptors on cardiac myocytes are vulnerable to LPS damage

LPS and the Heart

- Low levels of LPS depress cardiac myocyte contractility
- Reduces beta adrenergic responsiveness
- Induces Cell death in sepsis
- Genetic polymorphisms to TLR-4 more prone to severe infection
- LPS induces oxidative stress
GI Tract and Heart Failure

The importance of the gastrointestinal system in the pathogenesis of heart failure, Krsack, Andreas et al European Heart Journal (2005) 26, 2368–2374
doi:10.1093/eurheartj/ehi389

Chronic Heart Failure is a multi-organ disease
• Decreased blood perfusion creates intestinal ischemia ➔ altered permeability
• LPS triggers cytokine release from muscle tissue and organs
Microflora Disruption Leads To…

Leaky Gut and Intestinal Permeability
Low grade endotoxemia
Non Alcoholic Fatty Liver
Systemic inflammation signaling

Frazier, Thomas, H., Di Baise, John, K., McClain, Craig J., Gut Microbiota, intestinal permeability, obesity-induced inflammation, and Liver Injury J Parenter Enteral Nutr September 2011 vol. 35 no. 5 suppl 14S-20S
Options To Protect the Gut-Heart Connection

• L glutamine 2-5 grams
• Curcumin 500mg 1-2 capsules two times a day
• Probiotics strain specific
• Cat’s Claw (std. ext) 250mg 2-3 times a day
• Can add organic aloe juice two-4 ounces ounces to drink.
• Vitamin C 1-2000mg post exercise
Stress
Definition of Allostatic Load

- The wear and tear of the body and brain resulting from chronic over activity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge.

- Allostatic load results when the HPA axis is either overworked or fails to shut off after stressful events or when normal compensatory systems over react.

Central Mechanisms of Stress Induced Hypocortisolism

- Reduced biosynthesis of releasing factors or hormones
  - Hypothalamus
  - Pituitary
  - Adrenal gland
- Decreased or Increased target receptor sensitivity
- Hippocampal atrophy
- Hypersecretion of secretagogue with down-regulation of target receptors
Hypocortisolism: Global Physiologic Consequences
• Inadequate immune cell trafficking
• Inability to defend against pathogens
• Inadequate leukocyte trafficking
• Elevations of immune mediators (esp. hypocortisol states)
  ▪ Interleukins (IL-6 and 10) and TNFa
  ▪ Prostaglandins
  ▪ Lymphocytes
  ▪ Natural killer cells
  ▪ ANA antibodies
  ▪ Thyroid antibodies
Cardioendocrine System

- Accelerated progression of atherosclerosis, risk of MI and CHF
- Elevated inflammatory markers
  - PAI-1
  - Fibrinogen
  - HS-CRP
- Endothelial dysfunction and hypertension
- Enhancement of insulin resistance and hyperglycemia
Cardiovascular Disease and Cortisol

- CARDIA Study 2006
  - 718 black and white middle aged men
  - 6 salivary cortisol samples and coronary calcium scoring throughout one full day
  - Persons with cortisol slope scores in the flattest quartile had a greater likelihood of any coronary calcium than did those in the remaining quartiles adjusted for sex-race group, age, smoking, treatment for diabetes, systolic blood pressure, triglycerides, average cortisol, and educational attainment.
Physical Effects of Chronic Stress

1992

2000
• Common abnormal patterns
  ▪ Elevated
  ▪ Depressed
  ▪ Mixed

Diagnostic Assays:
Salivary Cortisol Patterns Matter
Salivary Cortisol and DHEA

Cortisol
Reference Range
1 Hour After Rising
7AM - 9AM:
0.27-1.18 mcg/dL
11AM - 1PM:
0.10-0.41 mcg/dL
3PM - 5PM:
0.05-0.27 mcg/dL
10PM - 12AM:
0.03-0.14 mcg/dL

DHEA 7am - 9am
Reference Range
191
71-640 pg/mL
DHEA: Cortisol Ratio/10,000
Reference Range
NR
115-1,188
Salivary Cortisol and DHEA

Cortisol
Reference Range
1 Hour After Rising
7AM - 9AM:
0.27-2.06 mcg/dL
11AM - 1PM:
0.03-0.77 mcg/dL
3PM - 5PM:
0.03-0.56 mcg/dL
10PM - 12AM:
0.03-0.50 mcg/dL

DHEA

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA 7am - 9am</td>
<td>72</td>
<td>14-277 pg/mL</td>
</tr>
<tr>
<td>DHEA / Cortisol</td>
<td>277</td>
<td>35-435</td>
</tr>
</tbody>
</table>
Significance in the Circadian Rhythm

• Flattening the cortisol curve
  ▪ Most predictive of stress related symptoms
  ▪ Most well studied
  ▪ Cortisol levels are up to 30% higher in endurance athletes.
  ▪ Cortisol can lead alterations lead to:
    Intensified
    Immune vigilance
    Fatigue
    IL-6 elevation

Diagnostic Assays:
Salivary Cortisol Patterns Matter
Stress

- Neuroexcitation
- Neurodegeneration
- Structural Plasticity

Brain

Gut

Immune

- Th1/Th2/Th17 balance
- Innate immunity
- Microglial activation
Neurons need to protect themselves from the excitotoxic effect of glutamate by reducing their input surface area.

NMDA Receptors
Adult Neurogenesis

- Adult neurogenesis refers to the production of new neurons in an adult brain
- Follows a similar complex multi-step process that starts with the proliferation of progenitor cells, followed by their morphological and physiological maturation.
- Ends with a fully functional neuron that is integrated into the pre-existing hippocampal network
Gut-Brain Interface

Brain
- Hypothalamus, PFC
- Locus coeruleus, amygdala
- Spinal cord and brain stem

Gut
- Enteric nervous system
- Enterochromaffin cells
- Tryptophan metabolism

Immune
Cardiopulmonary

- Primary pump function
- RSA and HRV
- Central driver of physiology

Vascular

- Single endothelial layer
- Architecture of circulation
- Major biological interface

Neuro

- SNS/PNS activity
- Amygala, PFC and Hypothalamus
- Mind Heart Connection
Emotions and the Heart

- New field of research - neurocardiology
- Demonstrates bidirectional information between CNS and Heart
- Mediated by lung function and peripheral nervous system
- Keys concepts: Resting Heart Rate and Heart Rate Variability
The heart communicates with the brain and body in four ways:

- *Neurological communication* (nervous system)
- *Biophysical communication* (pulse wave)
- *Biochemical communication* (hormones)
- *Energetic communication* (electromagnetic fields)
The "Heart Brain"

Brain
- Cortex
- Sub-cortical Areas
- Medulla
- Nodose Ganglion
- Dorsal Root Ganglion
- Spinal Cord (Sympathetic)
- Vagus Nerve
- Extrinsic Cardiac Ganglia (Thoracic cavity)

Heart
- Intrinsic Nervous System (Local Circuit Neurons)
- SA node
- AV node
- Sensory Neurites
- Sympathetic and parasympathetic outputs to muscles throughout the heart

Sympathetic
Parasympathetic
Afferent pathways
Sympathetic Overdrive

- Imbalance between sympathetic and parasympathetic nervous systems
- Direct innervation of sinus node
- Increased SNS due to affective disorders, chronic stress, neuroinflammation
- Leads to elevation in resting heart rate (RHR)
Mood and Heart Disease

• Up to 60% of patients with an acute coronary event experience symptoms of depression within the 12 months following the event

• Depression following acute MI doubles risk of mortality in the months following the acute event.

• Just having symptoms of depression at various times in the course of CHD doubles the risk of death, and that clinical depression is associated with an even higher risk.
• Separate studies showed that the risk of developing heart disease is significantly increased for people who impulsively vent their anger as well as for those who tend to repress angry feelings.

A. Siegman et al. J Behav Med. 1998; 21(4)
Mood and Heart Disease

• Depression linked to:
  – reduced adherence to treatment regimens
  – increased prevalence of smoking and diabetes
  – platelet dysfunction and coagulant processes
  – inflammatory processes
  – alterations in HPA axis
  – Autonomic nervous system (ANS) dysfunction
  – increased inflammation and plaque rupture

• Depression ➔ ↓vagal tone ➔ ↑inflammation and coagulation
Mood and Vagal Tone

- Increased IL-6 and TNFα
- Increased CRP
- Increased Fibrinogen
- Increased Resting Heart Rate
- Decreased Heart Rate Variability
Heart Rate Variability

- Even before the ECG, it was known that heart rate normally varies with respiration.
- The heart rate accelerates with inhalation and decelerates with exhalation.
- Physiologic respiratory sinus arrhythmia (RSA) can be demonstrated by plotting heart rate over time in resting supine subjects.
Heart Rate Variability

- Decreased HRV linked to cardiac events and mortality.
- Among healthy elderly subjects enrolled in the Framingham Heart Study, decreased HRV associated with increased major cardiac events.
Decreased Vagal tone and HRV

- Obesity
- Insulin resistance and diabetes
- Hypertension
- Hypercholesterolemia
- Depression and anxiety
- Heart failure
- Peripheral vascular disease
Neurodegeneration Hypothesis of Depression

Psychological Stress → Serotonin → Serotonin Receptors → Tryptophan

Physical Stress → Proinflammatory cytokines → IDO → Kynurenine → Kynurenate → Quinolinate

Antiinflammatory cytokines → Neurodegeneration

Major depression
Gut-Immune-Brain Supplements

**Brain**
- Tryptophan
- GABA
- St. John’s Wort
- L-theanine
- Holy Basil
- Magnolia/Phellodendron
- Melatonin
- Seditol
- Krill oil
- 5-HTP
- Neuromedulla gland
- Rg3
- Low Dose Naltrexone
- Phosphatidyl serine
- Tyrosine
- d-phenylalanine
- Fish oil
- αGPC/ALC/huperzine
- Minocycline
- Progesterone

**Gut**
- Milk Thistle
- Probiotics
- Digestive enzymes +/- HCL
- Zinc carnosine
- Mastic gum
- Glutamine/Aloe

**Immune**
- Cat’s Claw
- Nystatin
- Plant tannins
- Caprylic Acid
- Oral IgG powder
- Plant sterols
- Boswellia
- Thymic Extract
- DHEA
- UC-II
- Sialic Acid
- Astragalus
- DHA
- Estriol
Genetics of Heart Brain Pathology

• **APOE4**
  – Increased risk for Alzheimers and CVD
  – Key regulator of cholesterol transport
  – Enzymatic regulation of amyloid disposition in hippocampus and other memory centers

• **MTHFR**
  – Risk for treatment resistant depression and CVD
  – Underlies homocysteine and methionine pathway
  – Participates in neurotransmitter and hormone activation
  – Aids in ability to remove toxins
Apolipoprotein E, cardiovascular disease and cognitive function in aging women

Jae Hee Kang\textsuperscript{a,\ast}, Giancarlo Logroscino\textsuperscript{b}, Immaculata De Vivo\textsuperscript{a,\ast}, David Hunter\textsuperscript{a,\ast}, Francine Grodstein\textsuperscript{a,\ast}

\textsuperscript{a} Department of Medicine, Channing Laboratory, Brigham and Women’s Hospital, Harvard Medical School, 181 Longwood Ave., Boston, MA 02115, USA
\textsuperscript{b} Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA

Received 9 January 2004; received in revised form 5 May 2004; accepted 28 May 2004

demonstrated better cognition than the e3/3 group. Among APOE e4 carriers, baseline cognitive performance appeared particularly worse for those with cardiovascular conditions such as transient ischemic attack/carotid endarterectomy or untreated hypertension.
Apolipoprotein E, cardiovascular disease and cognitive function in aging women
Jae Hee Kang\textsuperscript{a,*}, Giancarlo Logroscino\textsuperscript{b}, Immaculata De Vivo\textsuperscript{a,b}, David Hunter\textsuperscript{a,b}, Francine Grodstein\textsuperscript{a,b}

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These epidemiologic studies are consistent with experimental findings that non-demented subjects with APOE e4 have more atrophy in the hippocampus (important for short-term memory) \cite{57} and decreased glucose metabolism in the temporal and parietal lobes \cite{43,44,56}. In addition, human neuropathological analyses and mouse models demonstrate that inheritance of an APOE e4 allele raises steady-state levels of amyloid beta in the brain, which accumulates in plaque deposits in Alzheimer disease \cite{22,48}. There is little information available regarding the cogni-
APOE4, Cognition and CVD

• APOE carriers with sub-clinical CVD are at high risk for decline in cognition
• Can be measured by serial MMSE, although additional cognitive scales may be required.
• Clinically significant if MMSE score drops by 4-5 points.
Proposed pathways involved in psychiatrically mediated states altering cardiovascular disease and outcomes

• Obesity
• Insulin resistance and diabetes
• Hypertension
• Hypercholesterolemia
• Depression and anxiety
• Heart failure
• Peripheral vascular disease

Endothelial dysfunction

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Supplements

CardioPulmonary
- Fish oil
- Magnesium taurate
- Hawthorn
- Carnitine
- Ribose
- CoQ10
- Vitamin K2
- Grape Seed Extract
- Aged Garlic Extract
- Vitamin C buffered
- Chelation
- Quercetin
- Bilberry
- Nattokinase

Vascular
- Tocotrienols
- Plant sterols
- Hawthorn
- Cocoa
- Aged Garlic Extract
- Fish oil
- Krill Oil
- ER niacin
- Milk peptides
- Arginine

Neuro
- Red Yeast Rise
- CoQ10
- Vitamin D
- Borage oil
- Pleo Muc
- Magnesium taurate
- HCSE
- Quercetin
- Pomegranate
- EGCG
- Huperzine/GPC
- Alpha Lipoic Acid
- Cistanche Tubulosa
- Ginkgo
- Vinpocetine
- Resveratrol
- Rg3
- αGPC
- Aged Garlic Extract
- Folate/B6/B12/MTHF
- St. John’s Wort
- SAMe
- Kavinace
- Holy Basil
- L-theanine
- Cerebrum compositum
- EGCG
- Breathing techniques