Managing Triad 2 and Triad 3 Relationships
The Role of Endotoxemia and Cardiovascular Health
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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

Gut-Immune-Brain
- Primary command and control
- Filtering, Defense and Repair
- Major physiologic interfaces
- Normal: Organized and secure
- Imbalanced: Disordered and unpredictable

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

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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 unvariable 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</td>
</tr>
<tr>
<td>67-70 bpm</td>
<td>1.07</td>
</tr>
<tr>
<td>71-74 bpm</td>
<td>1.07</td>
</tr>
<tr>
<td>75-79 bpm</td>
<td>1.07</td>
</tr>
</tbody>
</table>

P value < 0.001

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

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
• 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

GI Tract and Heart Failure

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 145-206

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–four 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.


Definition of Allostatic Load
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

- Immune System Dysfunction
  - 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

Immune System Dysfunction

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

- Common abnormal patterns
  - Elevated
  - Depressed
  - Mixed

Diagnostic Assays:
Salivary Cortisol Patterns Matter

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
    - IL-6 elevation
    - Fatigue

Diagnostic Assays:
Salivary Cortisol Patterns Matter
**Stress**
- Neuroexcitation
- Neurodegeneration
- Structural Plasticity

**Gut**
- Th1/Th2/Th17 balance
- Innate immunity
- Microglial activation

**Immune**

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**Neurons need to protect themselves from the excitotoxic effect of glutamate by reducing their input surface area.**

**NMDA Receptors**

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**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.

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**Gut-Brain Interface**
- Gut
  - Enteric nervous system
  - Enterochromaffin cells
  - Tryptophan metabolism
- Brain
  - Hypothalamus, PFC
  - Locus coeruleus, amygdala
  - Spinal cord and brain stem
- Immune

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**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
- Amygdala, 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)

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.
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 \( \downarrow \) vagal tone \( \uparrow \) 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
Triad Stacking

Genetics of Heart Brain Pathology

- **APOE**
  - 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

Gut-Immune-Brain Supplements

Neurodegeneration Hypothesis of Depression

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

Immune
- Cat’s Claw
- Nystatin
- Plant tannins
- Capsaicin
- Oral IgG powder
- Plant sterols
- Boswellia

Brain
- Tryptophan
- GABA
- St. John’s Wort
- L-theanine
- Holy Basil
- Magnolol/Phellodendron
- Melatonin
- Sedo
tol
- Kelp oil
- n-3 HTP
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- Seditol
- Krill oil
- 5-HTP
- Naltrexone
- Phosphatidyl serine
- Tyrosine
- d-phenylalanine
- Fish oil
- α-GPC/ALC/huperzine
- Minocycline
- Progesterone

Carbohydrates

Psychological Stress

Psychological Stress

Sero
tonin Receptors

Physical Stress

IDO

Kynurenine

Neurodegeneration

Major depression

Vascular

Neuro

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Gut

Brain
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.

Supplements

CardioPulmonary
- Fish oil
- Magnesium taurine
- Hawthorn
- Ribose
- CoQ10
- Vitamin K2
- Grape Seed Extract
- Red Yeast Rice
- Tocotrienols
- Plant sterols
- Hawthorn
- CoQ10
- Vitamin D
- Borage oil
- Magnesium taurine
- HSE
- Arterial inflammation
- Plaque rupture and acute coronary symptoms
- Endothelial dysfunction

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Triad 1
- Post-traumatic stress disorder
- Depression
- Psychiatric medication disorders
- Vagal tone
- Heart rate variability
- Heart rate recovery

Triad 2
- Neuroinflammation
- Neurodegeneration
- Obesity
- Insulin resistance and diabetes
- Hypertension
- Dyslipidemia
- Depression and anxiety
- Heart failure
- Peripheral vascular disease

Proposed pathways involved in psychiatrically mediated states altering cardiovascular disease and outcomes

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