NUTRITIONAL INTERVENTIONS TO REDUCE CARDIOMETABOLIC RISK

American College of Nutrition 2011

Stephen Sinatra, MD, FACC, FACN
Disclosures

Healthy Directions, L.L.C. – editor of monthly newsletter entitled Heart, Health and Nutrition
Nutrient supplement formulator for drsinattra.com
Bioenergetics is a study of energy transformations in living organisms used in the field of biochemistry, to reference cellular energy. Since every cell must have a way of obtaining energy, creative interventions to stabilize mitochondrial function and preserve ATP substrates will be a new metabolic medicine in the future.
MIRACLES IN THE MIDST
ANECDOTAL CASES OR VITAL CLUES
ABOUT A NEW THERAPY FOR HEART
DISEASE

Jim
Louise
Tommy

Helen
George
Catherine
Cardiomyocyte renewal (CR) & the Cold War
Body cell longevity max 10 years
Can metabolic cardiology “Buy” time for CR?

Reference:
Metabolic Cardiology
A New Emerging Field

- Congestive heart failure is an energy starved heart
- Role of ATP vs. oxygen in myocyte
- Pulsation of cell
- Decreased ATP concentration – serious defects in cellular metabolism

Cellular Mitochondria

- Powerhouse of cells
- 3500 - 5000 mitochondria – myocyte 35% of entire cell
- ATP formed in mitochondria transferred to cytosol to supply energy to cell
- Mitochondrial respiration - not all oxygen is converted to CO2 and water
- 3-5% of oxygen – toxic free radicals
- Mitochondrial DNA – no defense mechanisms
Mitochondria
Goddess of Disease

- Key to aging is decline/damage to mitochondria over time
- ATP energy production/hazardous waste – free radicals
- ATP production decreases about 40% with aging
- Cancer and mitochondrial DNA mutations increase with aging
- Centenarians and mitochondrial variants – protection from oxidative stress
- Mice with mitochondria that over express catalase – 20% increase in lifespan and protection from heart disease

Diastolic dysfunction (DD)
Parkinson’s Disease
Migraine
Autistic spectrum disorder
Fibromyalgia
Stain myopathy and cardiomyopathy
Mercury toxicity (IDCM)
Inborn errors of metabolism
Gulf War Syndrome
Nutrient Deficiencies in American Diet

- Inflammation processed foods and sugar
- Insidious depletion of nutrients vital to mitochondrial functioning
- Magnesium, Zinc, vitamins C, E, K and coenzyme Q10
The Perfect Storm
Mitochondrial Decay 2011

- Processed Diet
- Pharmaceutical Drugs – Toxicity/Nutrient Depletion
- Environmental toxins, chemicals - heavy metals
- Insecticides and pesticides
- Vaccinations
- Radiation – wireless and EMF
1800 MHz radio-frequency – oxidative damage to mitochondrial DNA in cultured neurons

24-hour exposure – Sig increase in levels of 8-hydroxyguanine (8-OHdG) a marker of DNA damage

Pretreatment with melatonin reversed changes
Mercury and the Heart

- Enormous increase in mean mercury concentrations (22,000 X) in biopsied specimens of 13 patients with idiopathic dilated cardiomyopathy (IDCM)
- Myocardial trace elements (TE) extraordinarily high for mercury and antimony (greater than 10,000 X) gold, chromium, and cobalt were also high vs. the controls
- Researchers speculate that adverse mitochondrial activity and subsequent ↓ myocardial metabolism, metabolic factors in IDCM
- Mercury – Mitochondrial toxin

Properly prescribed – 4\textsuperscript{th} leading cause of death in America

Most drugs cause depletion of vital nutrients i.e., statins – CoQ10; Birth control pills – B vits; ASA – Folate; Dilantin – Carnitine

Mitochondrial dysfunction often result of vitamin and mineral nutrient depletion

Many drugs mitochondrial toxins – NSAIDs, Viagra, Aricept, statins

Must find safer alternatives to pharmaceutical drugs to preserve mitochondrial function

Gulf War Syndrome

- Gulf War Syndrome – 1 in 4 of 200,000 veterans (GWVI)
- Chronic multi-systemic illness – fatigue, joint and muscle pain, headache, anxiety, dizziness, insomnia, immune and memory problems, depression, res & GI disorders
- Etiology – pesticides, ingestion of anti-nerve agent pills (pyridostigmine bromide or PB), emotional stress, vaccinations, burn pits, oil fires, EMF – radar, high powered radio transmitters
- As in the case of any chronic illness, the “perfect storm” knockout of our cellular integrity via mitochondrial toxicity
Dr. Beatrice Golomb – University of California, San Diego Medical School – Double blind trial of coenzyme Q10 vs GW syndrome

- 46 vets – 3.5 month study duration – crossover design
- Every veteran who took either high or low dose coQ10 improved!
- “For it to have been chance alone is under one in a million”
Veterans with GW Syndrome have same symptoms as those with mitochondrial disorders

CoQ10 supports mitochondrial function – makes perfect sense that Q10 alleviates symptoms of GW syndrome

Statins are mitochondrial toxins as well and patients intolerant to them have similar symptoms of GWS

Unnecessary use of statins – putting your body at war with itself

Must use statins with caution and only in population they help
Heart Disease

- 100,000 cases of new onset CHF – Great Britain
- 39% Idiopathic
- Nutritional – Mitochondrial Failure
- Inflammation
- Is there a biochemical/metabolic connection to heart disease
- Is ATP nutriceutical support a solution
Adenosine Triphosphate

ATP

Ribose

Three Phosphate Groups

Adenine
A major clinical challenge today is to develop strategies to preserve or improve heart pump function while maintaining cell viability. To achieve this goal, an understanding of the metabolic machinery for ATP supply and demand is required... Every event in the cell, directly or indirectly, requires ATP. Myocytes (heart cells) need ATP to maintain normal heart rates, pump blood and support increased work, i.e., recruit its contractile reserve. The myocyte needs ATP to grow, to repair itself and to survive. The requirement for ATP is absolute.”

Dr. Joanne Ingwall, Professor of Medicine (Physiology) Harvard Medical School

Dysfunctional energy in diseased hearts, angina, CHF, PTCA, CABG

Chronic CAD with ischemia and/or silent ischemia - severe energy deprivation occurs

Any intervention that will slow rate of ATP degradation and speed-up recovery rate will minimize heart damage and enhance cardiac function
CHF heart is energy starved, 30% of all energy lost.

Low intramyocardial ATP and reduced myocardial contraction.

Myocardial tissue may be restored significantly by oral supplements.

Coenzyme Q10, Carnitine, D-Ribose to restore ATP dynamics.
Nutraceuticals Supporting Cardiac Metabolism

**ATP Quantity**
- D-Ribose
  - The rate-limiting compound in synthesis of new ATP
    - *de novo* pathway
    - Salvage pathways

**ATP Turnover**
- L-Carnitine
- CoQ 10
Role of ATP in Heart Function

ATP

Myocardial Function
- Systolic contraction
- Diastolic relaxation

Ion pumps
- Electrochemical gradients
- Ca^{+2} pump

Biosynthesis
- Proteins & macromolecules
  - *de novo* ATP synthesis
ATP Utilization and Metabolism...

- 700 mg ATP in cardiac tissue
- At HR of 60 we utilization ≈ 70 mg/second
- 700 mg lasts 10 seconds ≈ about 10 heartbeats
- 86,000 beats/day = 6 million mg ATP utilized
- Myocardial ATP turns over ≈ 10,000 times/day!

“Just in Time” Production and Transport
A High \([\text{ATP}]\) is the Driving Force Underlying all Cellular Functions

As \([\text{ATP}]\) falls, one by one, cellular functional mechanisms become depressed.

Numbers in absolute values
ATP... A Renewable Energy Source

When oxygen, calories and co-factors are available…

ATP → Work + ADP + P_i → ADP + P_i [energy] → More ATP

When oxygen is not available (as in heart disease and/or exercise)…

ATP → Work + ADP + P_i → ADP + P_i [no energy] → no more ATP

PCr + ADP → Cr + ATP
ADP + ADP → ATP + AMP
AMP → Adenosine + P_i

Adenosine diffuses out of the cell and is lost
Ischemic Stress Depletes ATP and the Total Adenine Pool

Heart or Skeletal Muscle

- ADP
- ATP
- Myokinase

Plasma

- ADP
- $\text{P}_i$
- adenosine
- $5'$ Nucleotidase
- AMP Deaminase
- $\text{NH}_3 + \text{IMP}$

Net Loss of Purines

- $\text{P}_i + \text{Inosine}$
- Hypoxanthine

Washout of purines reduces total adenine nucleotide pool
The Solution

Restore the depleted energy substrates to the myocyte with nutraceutical support

- D-ribose
- Coenzyme Q10
- L-carnitine
- Magnesium
Heart Function

- 5M Americans CHF – 550,000 new cases/year
- 28% of men and women over age 45 have mild to moderate diastolic dysfunction with well preserved EF. (Redfield 2003)
- Women’s Health Report, June 2011 – A consensus by leading experts on the top 10 questions in cardiovascular care for women.
- Women predominant, lack of specific therapy, high mortality and morbidity. What are the most effective treatments for diastolic heart failure?

Reference: www.womenheart.org
2/3 of out patients referred for echo had DD – no symptoms of CHF

Echocardiogram from 1996 & 2005 > 36,000 persons had LVEF of 55% but a full 65.2% showed DD via mitral valve velocity

Dr. W. Jaber, senior author “Clinicians don’t pay much attention to it because they don’t know what to do with it” and “moderate to severe should not be taken lightly”

Authors offered no solutions – The only remedy is to restore energy substrates to myocardium – or – a metabolic cardiology program. (Sinatra)

More common in women with hypertension, IHSS, MVP, and infiltrative cardiomyopathy

Diastolic dysfunction early sign of myocardial failure despite adequate systolic function

Diastolic function requires more cellular energy than systolic contraction as higher concentrations of ATP required to activate calcium pumps necessary to facilitate cardiac relaxation and diastolic filling

Statin - cardiomyopathy

Improved diastolic function and compliance with supplemental CoQ10

2,3-dimethoxy-5-methyl-6-decaprenil-1,4-benzoquinone
The History of CoQ10

- 1957 – CoQ10 first isolated from beef heart by Frederick Crane
- Mid-1960s – Professor Yamamura (Japan) is the first to use CoQ7 (related compound) in congestive heart failure
- 1972 – Dr. Littaru (Italy) and Dr. Folkers (United States) document a CoQ10 deficiency in human heart disease
- Mid-1970s – Japanese perfect industrial technology of fermentation to produce pure CoQ10 in significant quantities.
- 1977 – Peter Mitchell receives Nobel Prize for CoQ10 and energy transfer
1980s – Enthusiasm for CoQ10 leads to tremendous increase in number and size of clinical studies around the world

1985 – Dr. Per Langsjoen in Texas reports the profound impact CoQ10 has in cardiomyopathy in double blind studies

1990s – Explosion of use of CoQ10 in health food industry

1992 – CoQ10 placed on formulary at Manchester Memorial Hospital, Manchester, CT

1996 – 9th international conference on CoQ10 in Ancona, Italy. Scientists and physicians report on a variety of medical conditions improved by CoQ10 administration. Blood levels of at least 2.5 ug/ml and preferably higher required for most medical purposes
- 1996-1997 – Gel-Tec, a division of Tishcon Corp., under the leadership of Raj Chopra, develops the “Biosolv” process, allowing for greater bioavailability of supplemental CoQ10 in the body
- 1997 – CoQ10 hits textbooks of mainstream cardiology
- 1997-2004 – Continued research into role of CoQ10 in cardiovascular health and mitochondrial diseases
- 2004 – Canadian government places ubiquinone on statin labels as a precaution
- 2005 – Blood levels of CoQ10 much higher when taken twice daily compared to once-a-day dosing of the same amount
- 2006 – Introduction of Ubiquinol QH™ by Kaneka
- 2008 – Am Journal of Cardiology – Blood levels of CoQ10 in CHF an index of longevity
Figure 1. Axial view schematic of the heart
L-carnitine

- Trimethylated amino acid-like cofactor for the transport of free long-chain fatty acids in the mitochondrial matrix where beta-oxidation occurs for cellular energy production

- Originally isolated from meat in 1905. Its crucial role in metabolism was discovered in 1955

- Carnitine deficiencies in humans – 1973
Like CoQ10, carnitine deficiency is usually not a factor in a healthy, well-nourished population consuming adequate animal protein.

Aging, genetic defects, cofactor deficiencies (B6, magnesium, folic acid, iron, vitamin C) liver or kidney disease, anticonvulsant drugs – dietary considerations can cause carnitine deficiencies.

The extreme of mild deficiency and tissue pathology are revealed in the population.
L-carnitine and Diet

- Found in muscle
  - Sheep
  - Lamb
  - Cattle
  - Pig

- Very low in grains, cereals, fruits, and vegetables

- Like Coenzyme Q10, low in vegetarians
L-carnitine Physiology

- Beta oxidation of fatty acids – in mitochondria
- 60% of heart energy metabolism of fatty acids
- Removal of lactic acid and other toxic metabolites from blood
- Ammonia detoxification
- L-carnitine, Acetyl-L-carnitine, Propionly-L-carnitine – Also function as antioxidants
- Next generation – Aminocarnitines
L-carnitine Clinical Considerations

- Heart Disease - CHF, Arrhythmia, Blood Pressure
- Cardiovascular Prevention - Increase HDL, Decrease Triglycerides
- Physiological and Mental Performance, CFS, Energy and Aging
- Liver Disease (ETOH)
- Kidney Disease (Dialysis)
- Male Infertility
- TPR and Malnutrition
- Peripheral Vascular Symptoms (Leg Cramps)
- Mitochondrial Muscle Diseases
Summary of L-carnitine and Coenzyme Q10 in CV Disease

Unusual ability to enhance fatty acid oxidation in cells while removing excess harmful substances such as acyl groups and free radicals from basement membranes. CoQ10 acts like the spark plug to ignite the energy process in the mitochondria to form ATP or the energy of life. L-carnitine acts like a freight train shuttling in and out crucial fatty acids that are burned as fuel. Both these nutrients, while supporting cardiovascular function, preserve the inner mitochondrial membrane and delay the aging process at the same time.
D-ribose is a naturally occurring pentose sugar that rebuilds the energy stores in the cell. These 3 compounds: Ribose, CoQ10 and Carnitine, form the “Triad of Metabolic Cardiology.” Together they act like “Rocket Fuel.”
D-ribose

- Loss of purines in ischemic situation
- Slow process to replace adenine pool
- D-ribose used by cell to manage cellular energy restoration
- If D-ribose not available energy pool cannot be restored
- Human heart – it may take up to 100 days to restore ATP via *de novo* synthesis

*Rate limiting step in salvage and synthesis of ATP is availability of D-ribose*
Canine Model

- Aortic Pressure
- Pleural Pressure
- L.V. Pressure
- Sonomicrometer

- Balloon Occluder
- Atrial Pacer
- Coronary Sinus Catheter
- R.V. Biopsy Catheter

Correlation Between ATP Level and Diastolic Function

- Ischemia - dramatic drop in ATP concentration
- Decreased ATP corresponds to loss of diastolic function
- Administration of D-ribose – improvement in diastolic function
Complexity of cardiac energy metabolism is clear

Failing/ischemic heart – loss of energy substrates

↓ATP -- ↓diastolic function

Must restore energy reserve – ribose

Enhance ATP turnover with carnitine & Q10

All promote cardiac energy metabolism, restore ATP, ↑heart function
Mitochondrial restoration and energy pool support is the metabolic solution

Metabolic therapy is often underutilized Rx for cardiac disease

Targeted metabolic therapy will improve myocardial metabolism

Metabolic cardiology provides great hope for future Rx for cardiovascular disease


