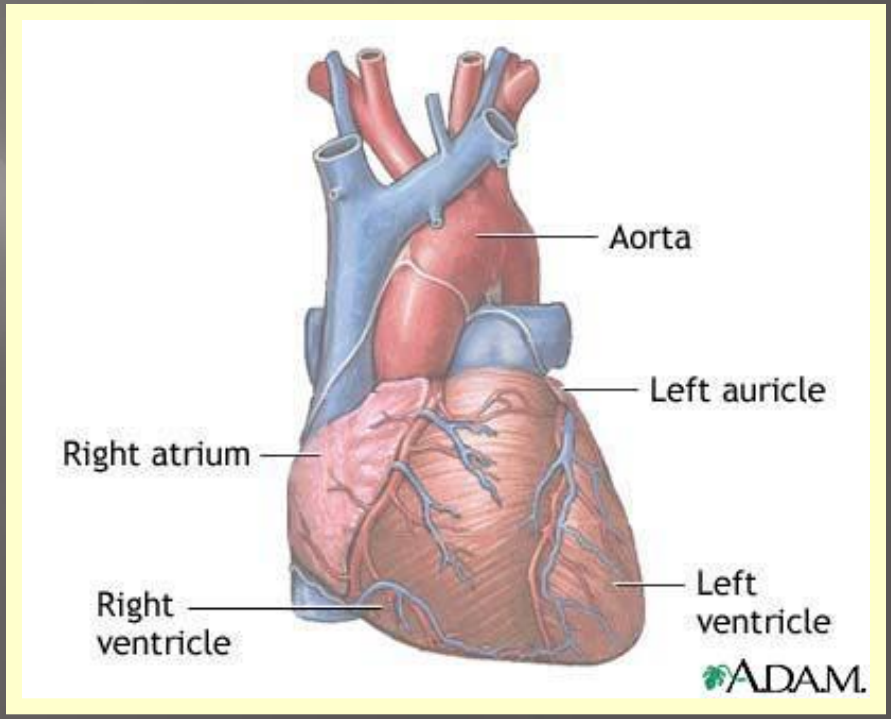
NUTRITIONAL INTERVENTIONS TO REDUCE CARDIOMETABOLIC RISK

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 drsinatra.com

Bioenergetic Medicine

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

New Clues in the Mystery of Heart Muscle Renewal

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

Reference:

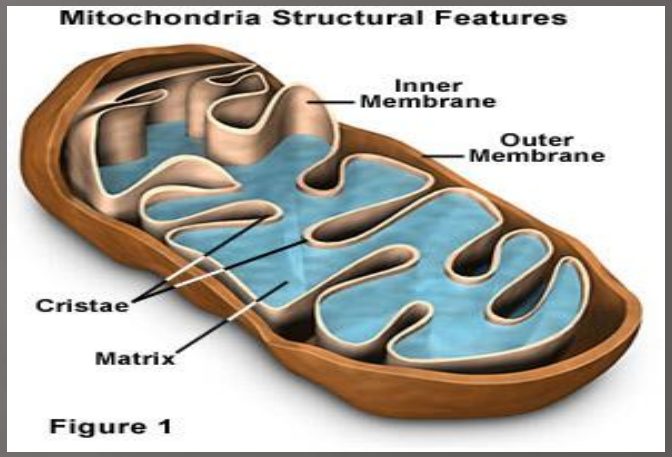
Bergmann O, Frisen J, et al. Evidence for cardiomyocyte renewal in humans. Science 2009;361(1):86-88.

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

Reference: Bashore TM, Magorien DJ, Letterio J, Shaffer P, Unverferth DV. Histologic and biochemical correlates of left ventricular chamber dynamics in man. *J Am Coll Cardiol.* 1987;9:734-42.

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 CO_2 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

Reference Shriner SE. Science. 308:1909-1911.2005

A Sampling of Mitochondrial Dysfunction and Illness

- 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

Biological Effects of Wireless Communications

- 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

Reference: Frustaci A, et al. Marked elevation of myocardial trace elements in idiopathy dilated cardiomyopathy with secondary dysfunction. J. Am. Coll. Cardiol 1999;33:1578-83

Pharmaceutical Drugs

- Properly prescribed – 4th 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

Ames BN, Atamna H, Killilea DW. Mineral and vitamin deficiencies can accelerate the mitochondrial decay of aging. Mol Aspects Med. 2005 Aug-Oct;26(4-5):363-78.

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

Coenzyme Q10 and Gulf War Syndrome

- 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”

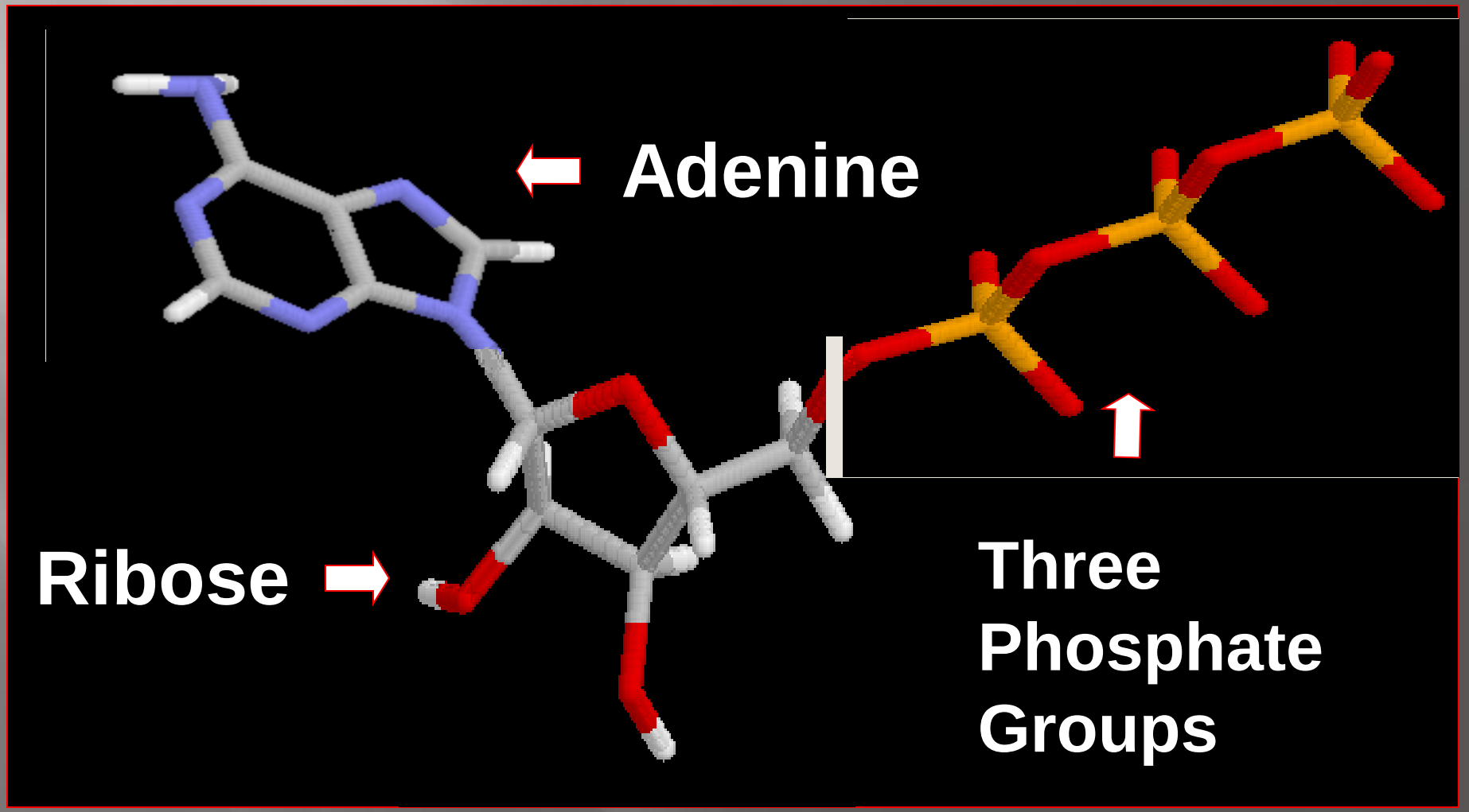
GW Syndrome and Stains Common Ground

- 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



ATP and Myocardial Function

"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

Reference: Ingwall JS. ATP and the heart. Boston, MA:Kluwer Academic Publishers, 2002.

Bioenergetics & the Heart

- 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

Bioenergetics & the Heart Part II

- 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

Nutriceuticals Supporting Cardiac Metabolism

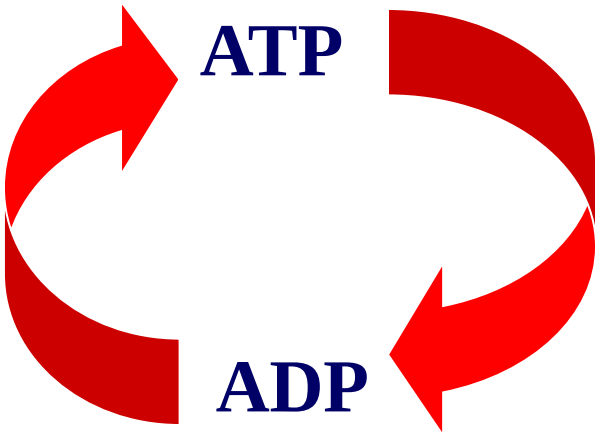
ATP Quantity

- **D-Ribose**

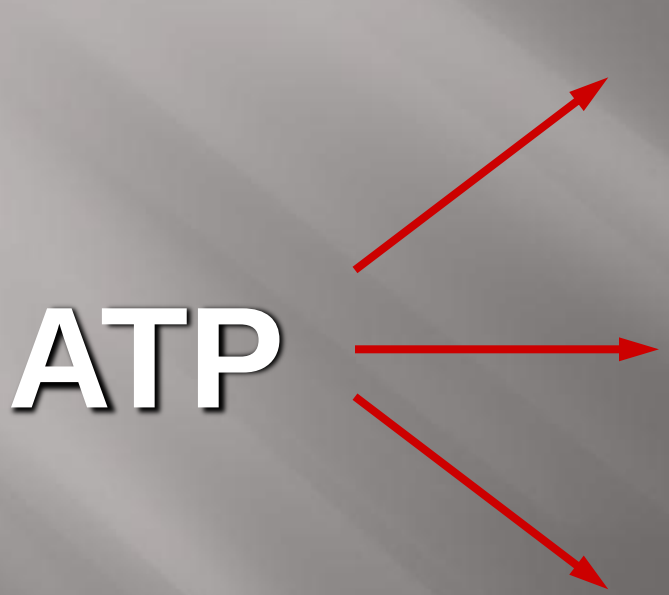
  The rate-limiting compound in synthesis of new ATP
  - *de novo* pathway
  - Salvage pathways

ATP Turnover

- **L-Carnitine**
- **CoQ 10**



Role of ATP in Heart Function



Myocardial Function
- Systolic contraction
- Diastolic relaxation

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

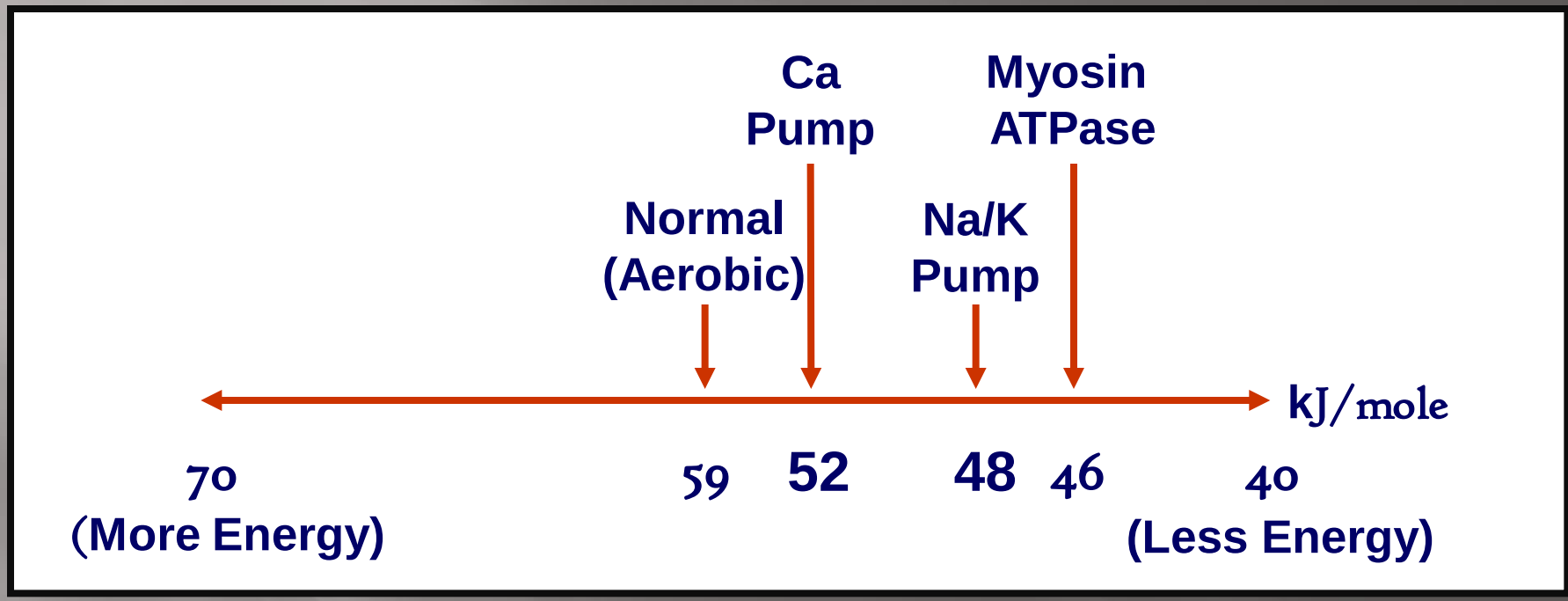
Biosynthesis
- Proteins & macromolecules
- *de novo* ATP synthesis

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 [ATP] is the Driving Force Underlying all Cellular Functions



As [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

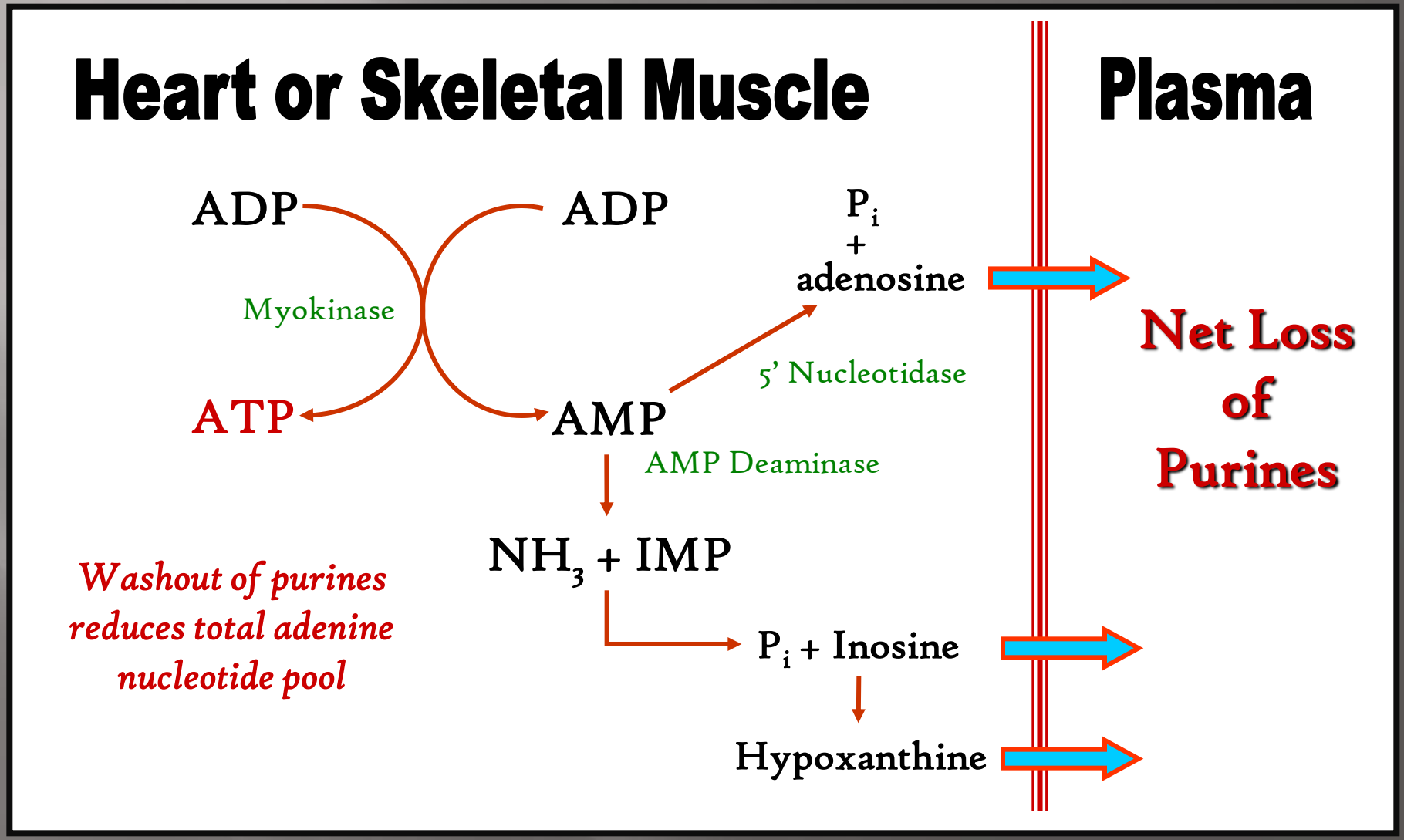
PCr + ADP ⟶ Cr + ATP

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



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

Diastolic Dysfunction and Mortality June 2011

- 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)

Ref: Halley, et al., Mortality rate in patients with diastolic dysfunction and normal systolic function. Arch Intern Med 2011:171;1082-1087.

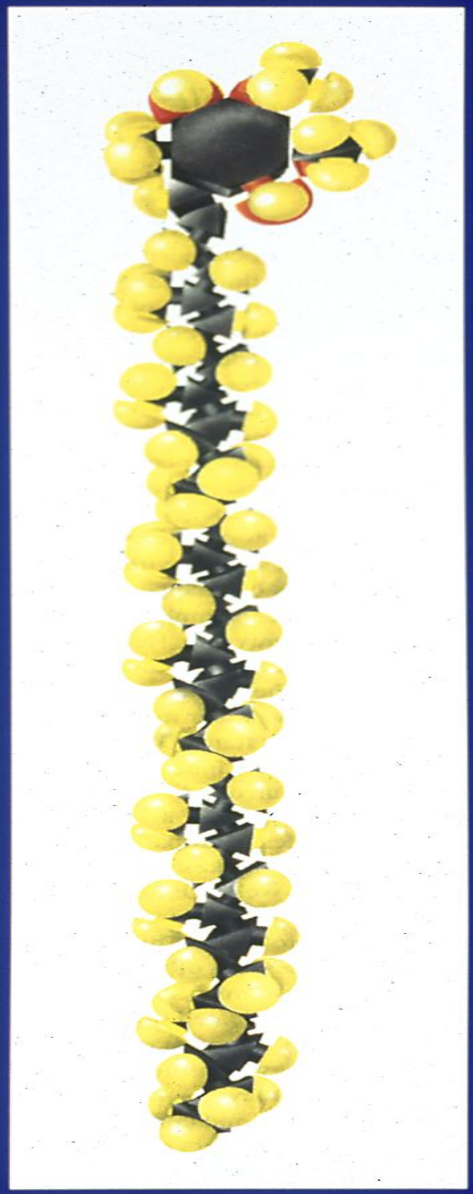
Sinatra ST. Metabolic cardiology: the missing link in cardiovascular disease. Altern Ther Health Med. 2009 Mar-Apr;15(2):48-50. Review.

Coenzyme Q10 and Diastolic Dysfunction

- 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

Reference: Langsjoen PH et al. *Molecular Aspects of Medicine* 15, 1994 265-272. Proceedings from the Third Conference of the International CoEnzyme Q10 Association, London, Nov. 2002.

CoEnzyme Q10



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

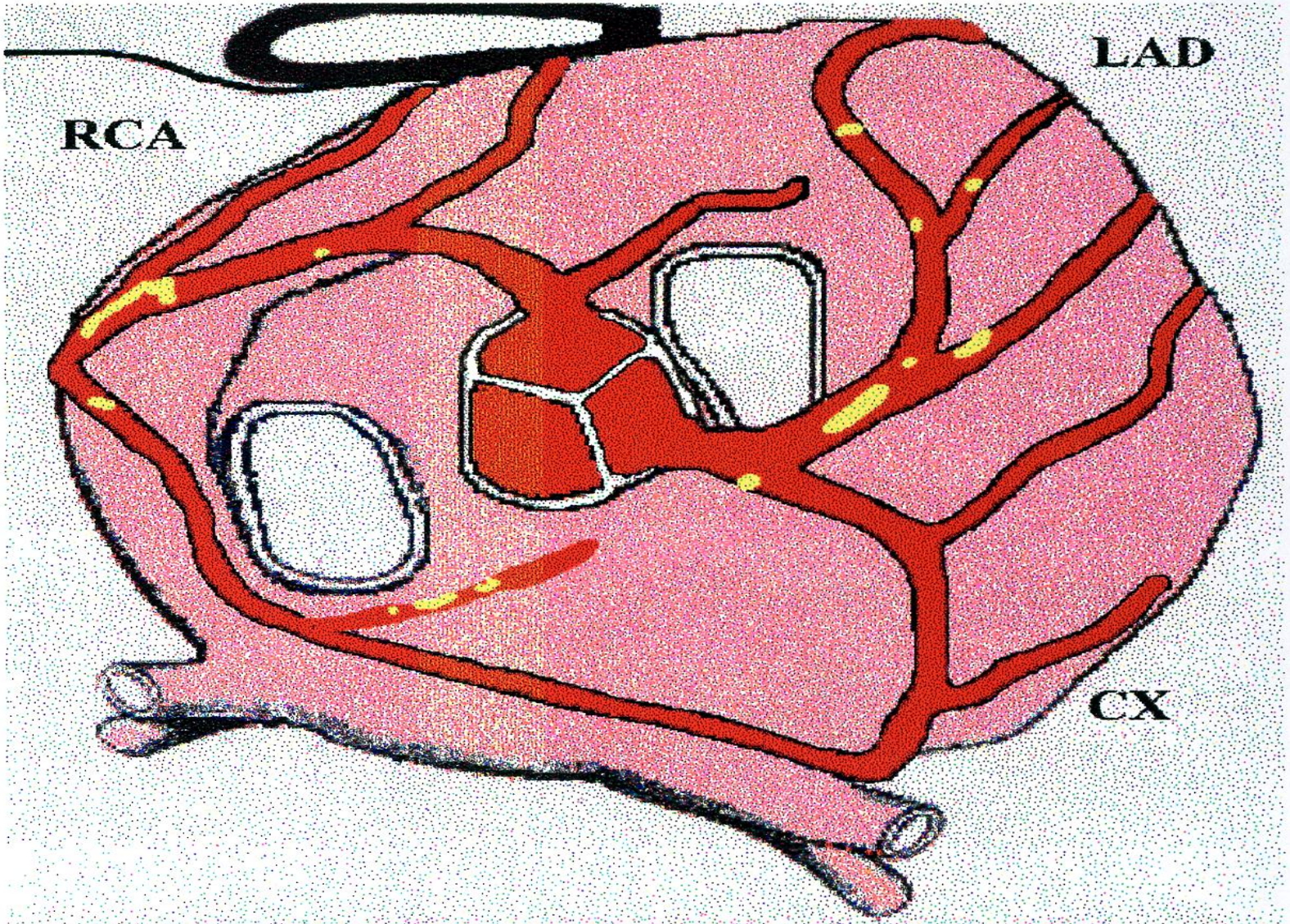


Figure 1. Axial view schematic of the heart

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

L-carnitine cont'd

- 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: the New "Kid" on the Block

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

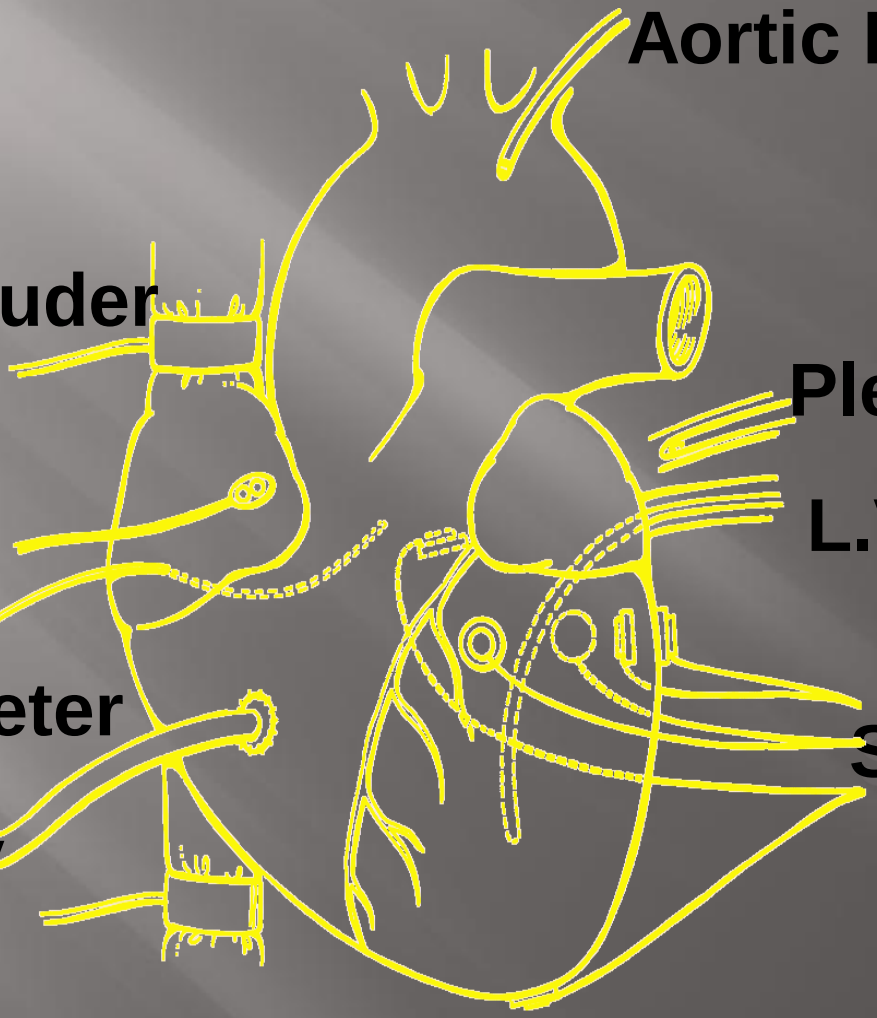
"Rocket Fuel."

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

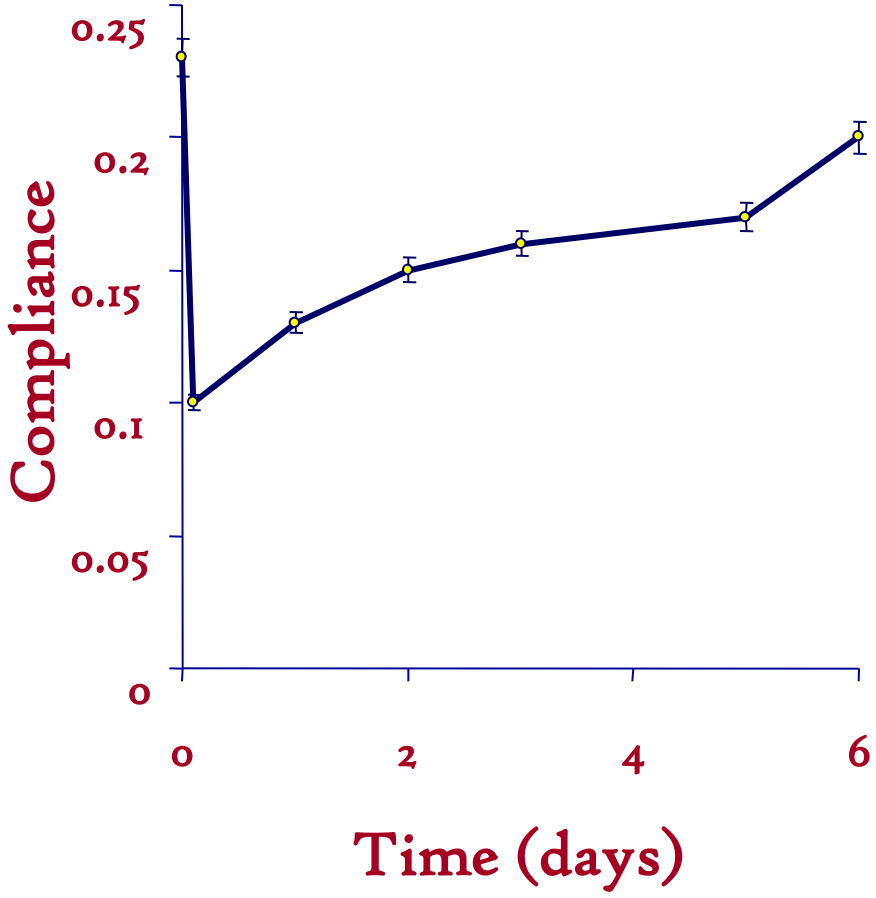


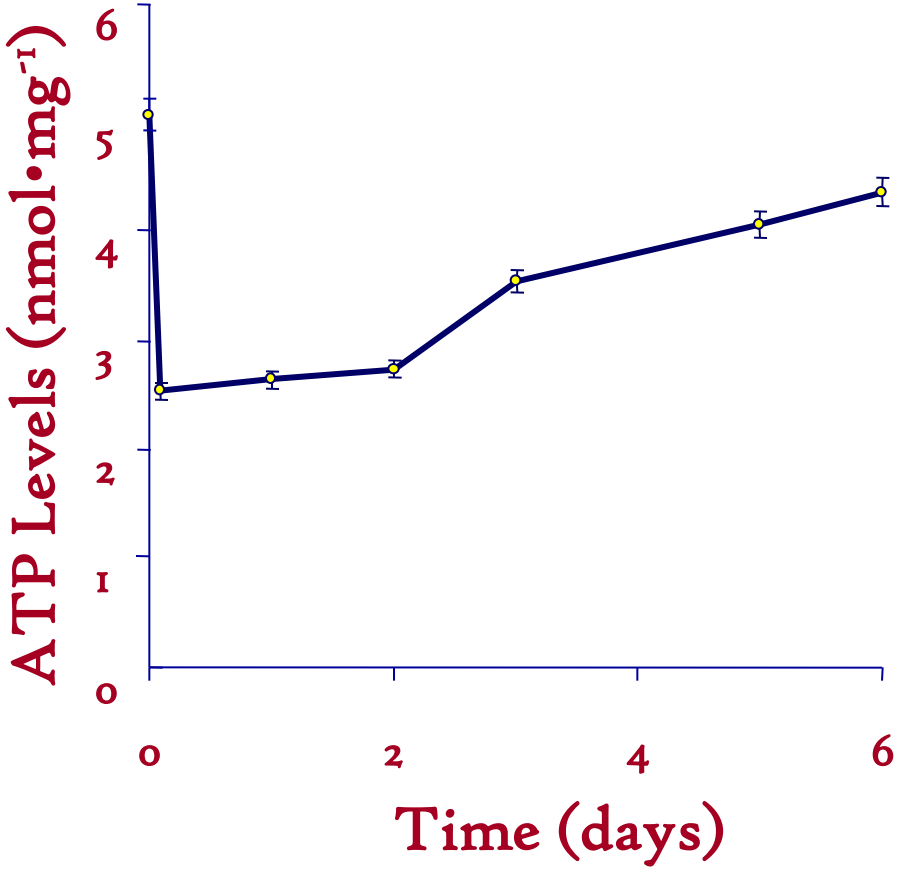
Reference: St. Cyr JA, et al. Data on File.

LV Compliance

Myocardial ATP Levels

Following Global Ischemia





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

Metabolic Cardiology

- 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

Metabolic Cardiology - Conclusion

- 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

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