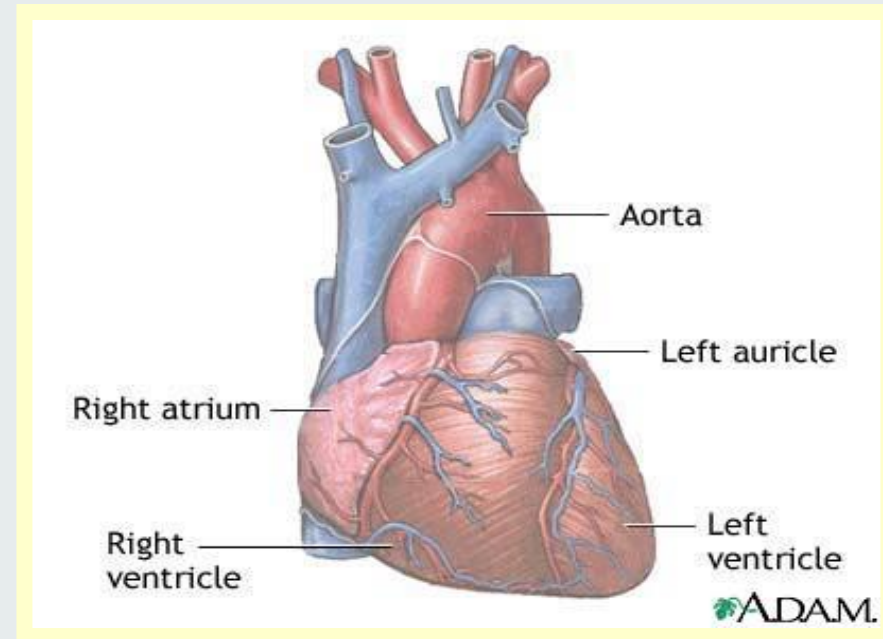


# Healing the Heart

*Metabolic Cardiology  
A4M 2015  
Las Vegas, NV*



**Stephen Sinatra, MD, FACC, FACN**

# Healing the Heart

## HRV/ Heart-Brain Hotline

- HRV – What the heart can teach us about the mind
- HRV reveals the truth about the ANS
- The ANS is involved in all diseases
- Must support the ANS – create balance
- Improving parasympathetic tone is the key ingredient in attenuating illness

# Healing the Heart Modalities

- Non-inflammatory healthy fat, lower carb, mild to moderate protein diet
- Alleviate emotional toxicity
- Positive intention – optimism vs pessimism
- Move with exercise, yoga, Qui Chong, Tai Chi
- Grounding
- Telling the truth (misrepresentation – a betrayal of the ANS)
- Targeted nutritional supports – omega 3's, higher DHA over EPA, MV/MM formulation, vitamin K2, ATP support – metabolic cardiology
- Metabolic cardiology – the awesome foursome – coenzyme Q10, L-carnitine, D-ribose, and magnesium

# 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.

# Metabolic Cardiology

## A New Paradigm for the Prevention and Treatment of Heart Disease

**Me-tab-o-lism** (m\_tab'\_liz'm), n. The biochemical changes in the living cells by which energy is provided for vital processes and activities.

# Metabolic Therapy for Heart Disease

- Metabolic Rx – the administration of a substance found naturally in the body to support a metabolic reaction in the cell.
- Example – a substance given to achieve greater than normal levels in the body to drive an enzymatic reaction in a preferred direction, or a substance given to correct a deficiency of a cellular component.
- Metabolic therapy is frequently the opposite of standard pharmaceutical Rx that block, rather than enhance.
- Cellular processes. Example – beta blockers, calcium blockers, ACE inhibitors and statins.
- Metabolic therapy does not have profound physiological effects like increase or decrease in blood pressure or heart rate.

# Metabolic Substances that Positively Impact the Heart

- Glucose – insulin – potassium – increase myocardial glycogen and ATP
- Magnesium – 300 enzymatic reactions improves energy in cells especially in recent infarcted myocardium
- Coenzyme Q10 – Lipid soluble antioxidant plays vital role in cellular ATP production.
- Carnitines – Support beta oxidation of fatty acids in mitochondria for energy production.
- D-ribose – Energy substrate to support oxidative phosphorylation in myocyte.

Conclusion – all improve cellular energy production and support myocardial function especially in the settings of ischemia and congestive heart failure.

# Miracles in the Midst Anecdotal Cases or Vital Clues About a New Therapy for Heart Disease

Jim



Helen

Louise



George

Tommy

Catherine





# New Clues in the Mystery of Heart Muscle Renewal

- Cardiomyocyte renewal (CR) & the Cold War
- Myocardium 40% after decades
- 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.

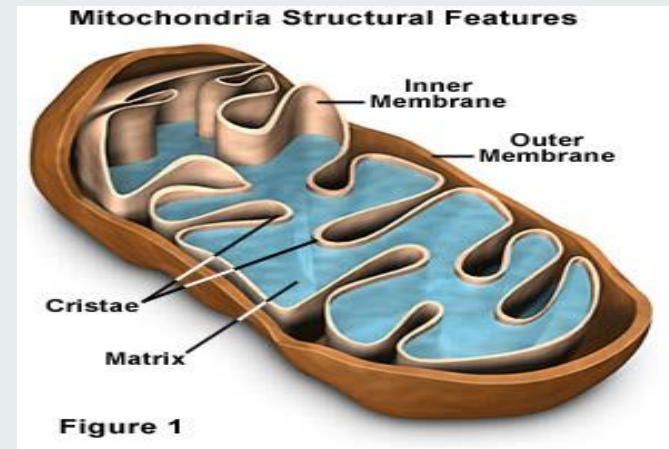
# Metabolic Cardiology

## 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<sub>2</sub> 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

# 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 2015

- 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 idiopathic dilated cardiomyopathy with secondary dysfunction. J. Am. Coll. Cardiol 1999;33:1578-83

# Pharmaceutical Drugs

- Properly prescribed – 4<sup>th</sup> 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

Reference: 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
- The “perfect storm” of 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

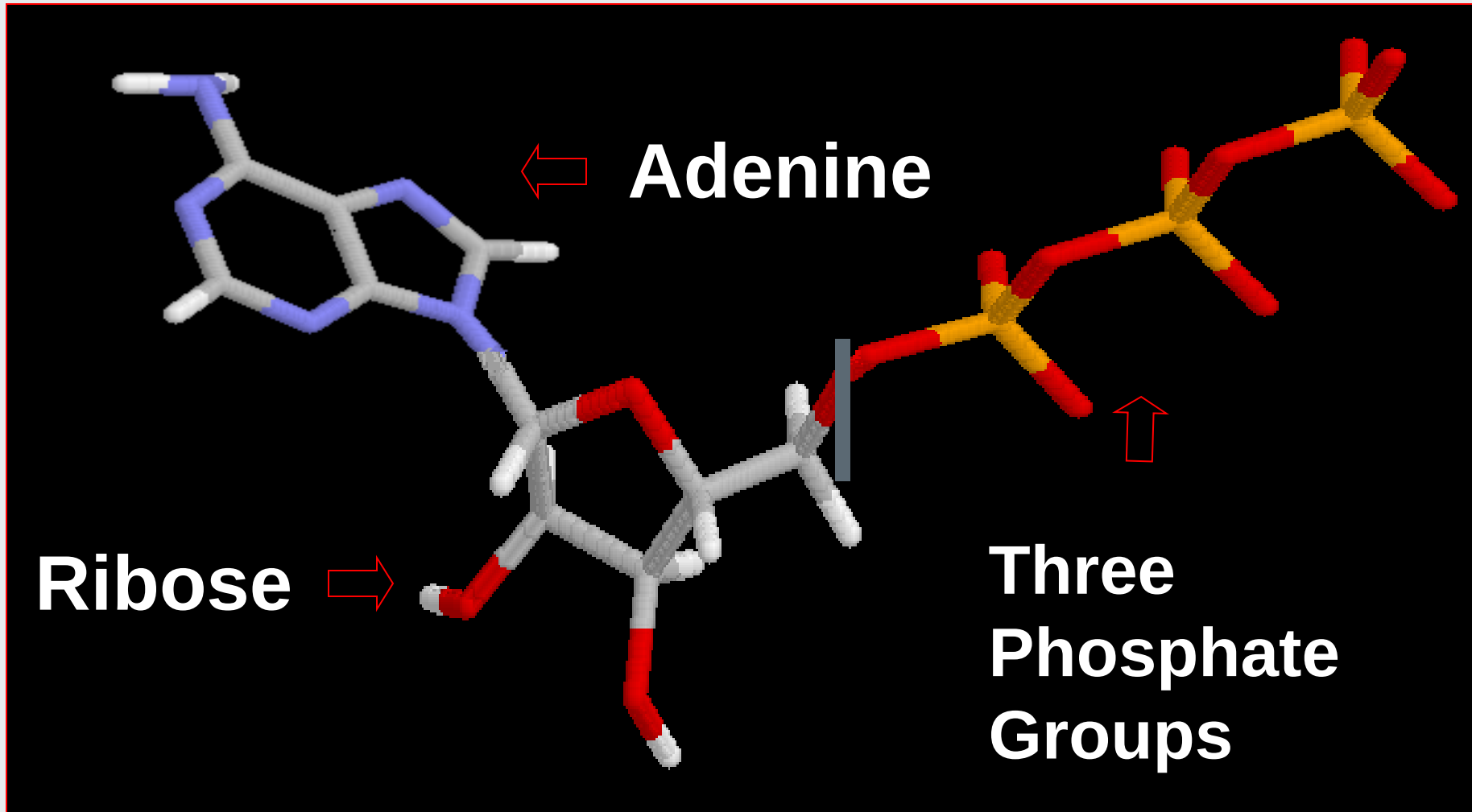
- 100,000 cases of new onset CHF – Great Britain
- 39% Idiopathic
- Nutritional – Mitochondrial Failure
- Inflammation
- Is there a biochemical/metabolic connection to heart disease
- Is ATP nutraceutical support a solution

# Bench to Bedside

- Failing myocardium – although viable and dysfunctional, is not irreversibly damaged
- Heart failure is an energy-starved heart running out of fuel
- Rx – support the cardiomyocyte
- Cellular biochemistry or bringing the conversation from the bench to the bedside is the challenge



# 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*

# 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

# Nutraceuticals Supporting Cardiac Metabolism

## ATP Quantity

### ➤ D-Ribose

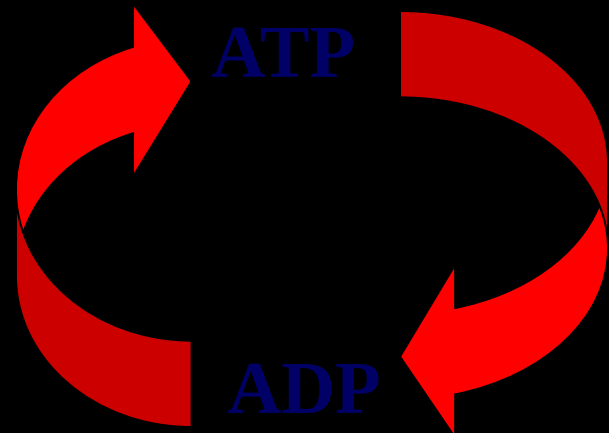
The rate-limiting compound in synthesis of new ATP

- *de novo* pathway
- Salvage pathways

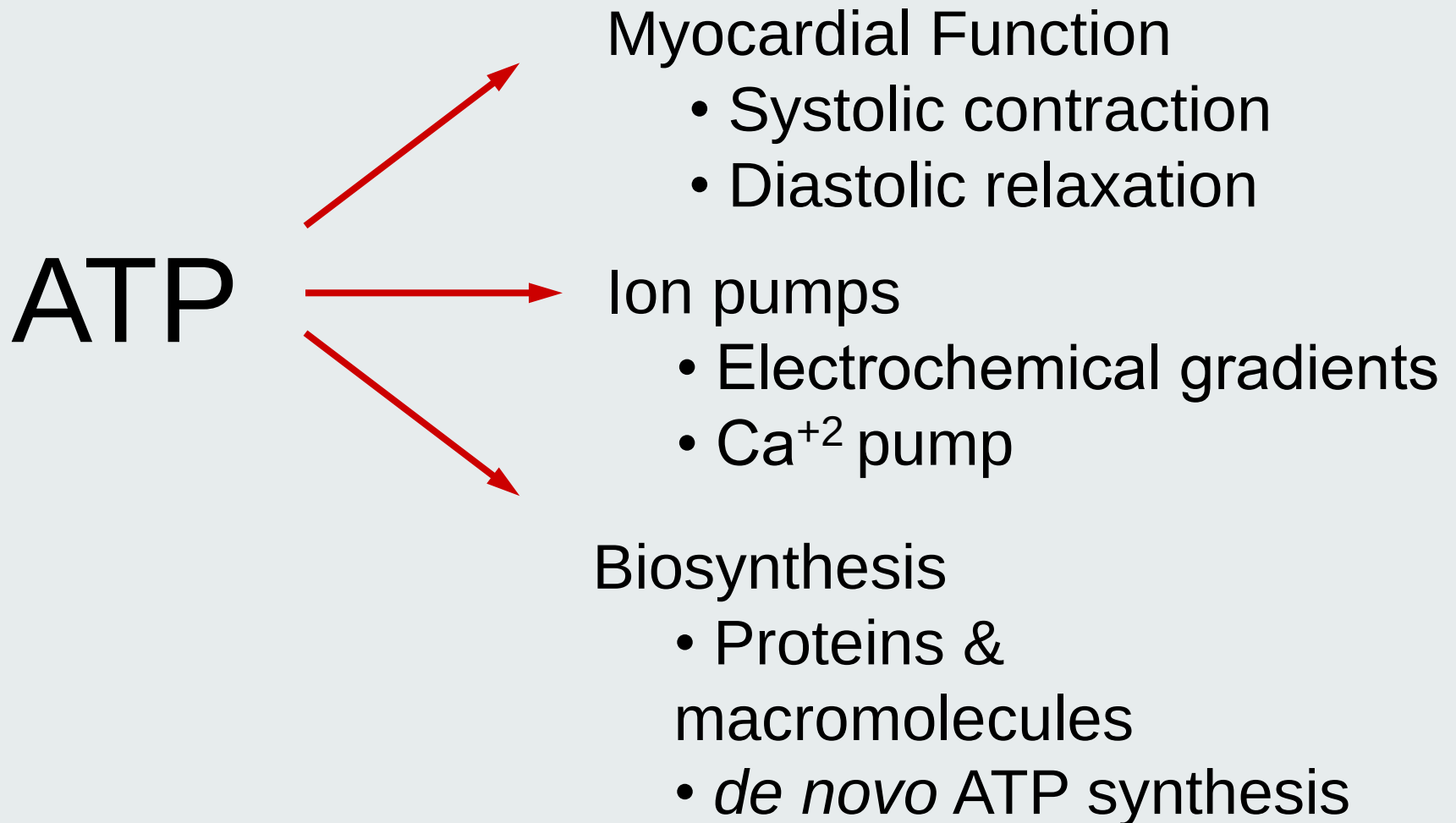
## ATP Turnover

### ➤ L-Carnitine

### ➤ CoQ 10



# Role of ATP in Heart Function

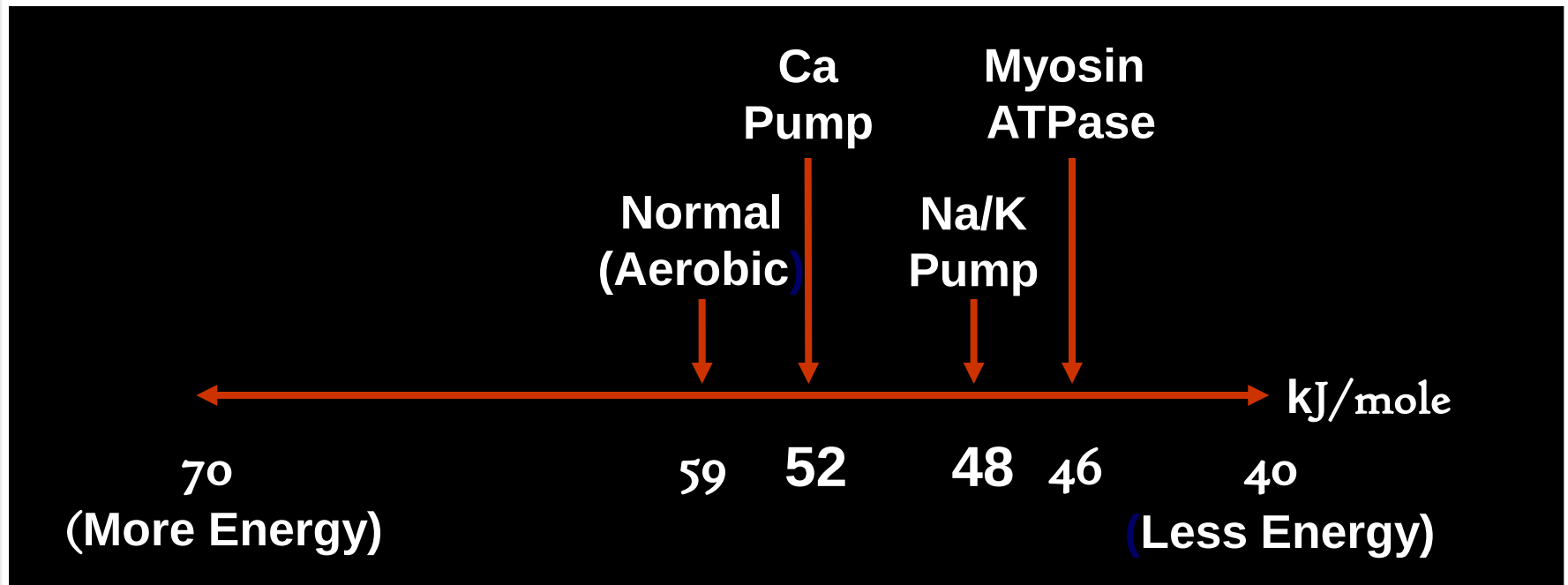


# ATP Utilization and Metabolism...

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

**“Just in Time” Production and Transport**

# A High [ATP] is the Driving Force Underlying all Cellular Functions

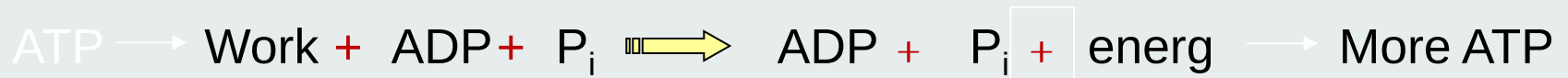


*As [ATP] falls, one by one, cellular functional mechanisms become depressed.*

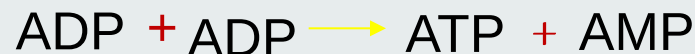


# ATP... A Renewable Energy Source

*When oxygen, calories and co-factors are available...*



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

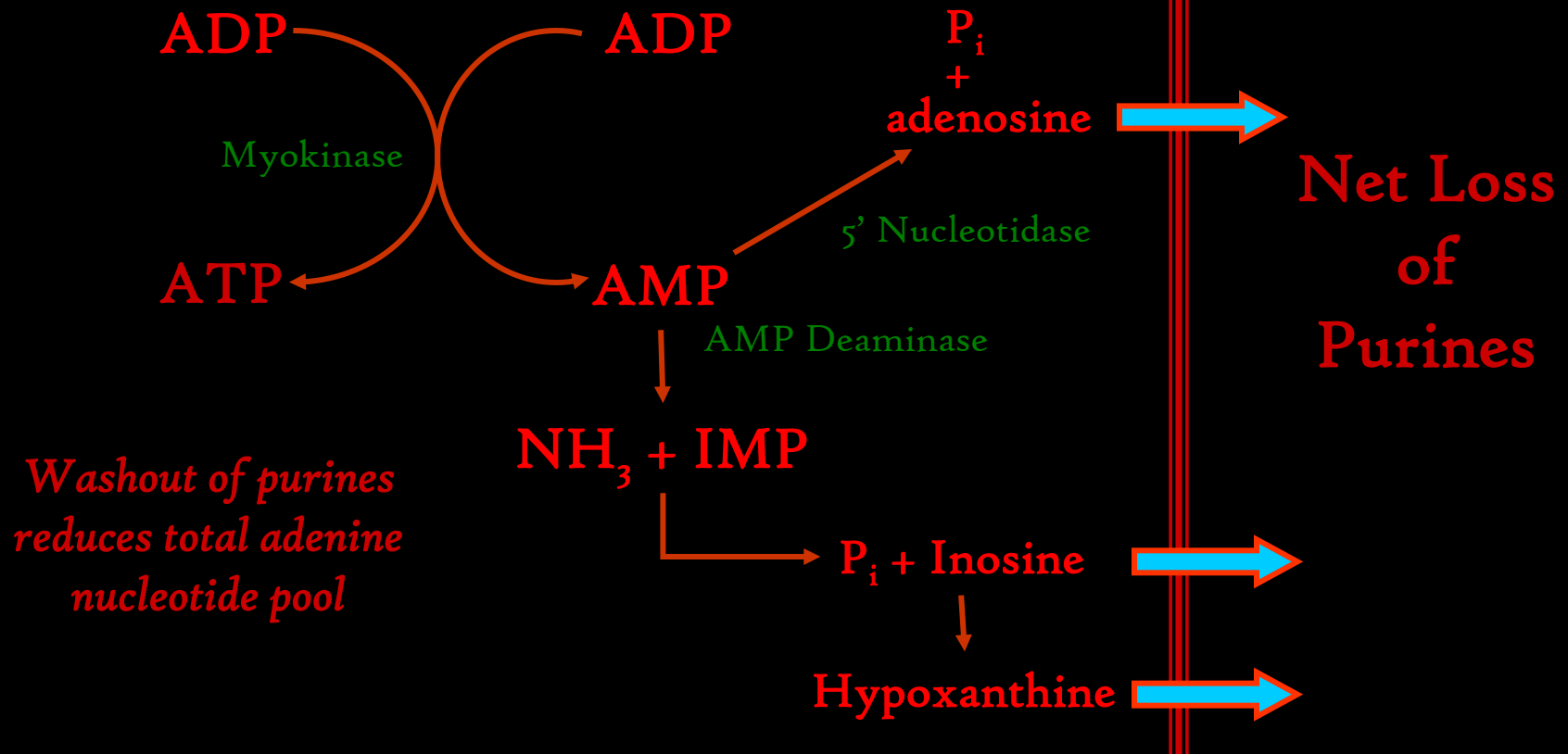


Adenosine diffuses out of the cell and is lost

# Ischemic Stress Depletes ATP and the Total Adenine Pool

Heart or Skeletal Muscle

Plasma



# 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](http://www.womenheart.org)

# 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

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.

# 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)

### Reference:

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.

# Diastolic Dysfunction

## *A Growing Epidemic?*

- Risk of diastolic and systolic CHF >40 years is 20% -- this is alarmingly high and in excess of many conditions associated in aging, JAMA 2003
- Progression of widespread DD and risk of heart disease failure occurring in advancing age and detected in healthy people, JAMA 2011
- Diastolic dysfunction and atrial fibrillation in patients undergoing cardiac surgery, AJC 2011
- \*\*\*Challenge to find precise physiological mechanism and a therapeutic solution – All studies inc Arch Int Med 2011

# DD Physiological Mechanisms

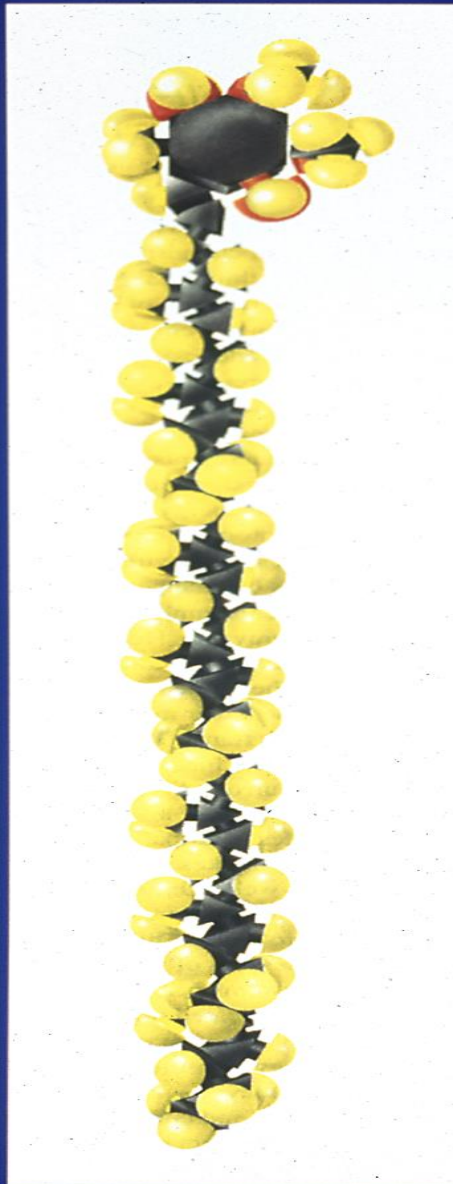
- The energetic imbalance of diastolic heart failure is characterized by an increase in energy demand and a decrease in energy production, transfer and substrate utilization resulting in an ATP deficit
- Biopsies of heart tissue in heart failure patients reveal diminished quantities of ATP in the mitochondria, AJC 1987
- Similar energetic adaptations in atrium may contribute to atrial fib, Am J Physiol 2003



# Diastolic Dysfunction – The Solution

- Randomized controlled trial, 300 mg of Coenzyme Q10 reduced plasma pyruvate/lactate ratios and improved endothelial function via reversal of mitochondrial dysfunction in patients with ischemic LV systolic dysfunction, Artherosclerosis 2011
- Improved diastolic function and compliance with CoQ10, AJC 2004
- Rx options that incorporate metabolic interventions targeted to preserve ATP energy substrates (D-ribose) or accelerate ATP turnover (L-carnitine and Coenzyme Q10) are indicated for at-risk populations and patients undergoing cardiovascular surgery
- Metabolic cardiology – providing essential raw materials that support cellular energy substrates needed by mitochondria to rebuild feeble ATP levels, Altern Ther Health Med 2009

# CoEnzyme Q10



**2,3-dimethoxy-5-methyl-6-decaprenyl-  
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 – 9<sup>th</sup> 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
- 2011 – Q10 reduces oxidative damage in Down’s Syndrome
- 2013 – CoQ10 Rx for CHF (2008, New Zealand)

# Lisbon, Portugal

## Heart Failure Congress, 2013

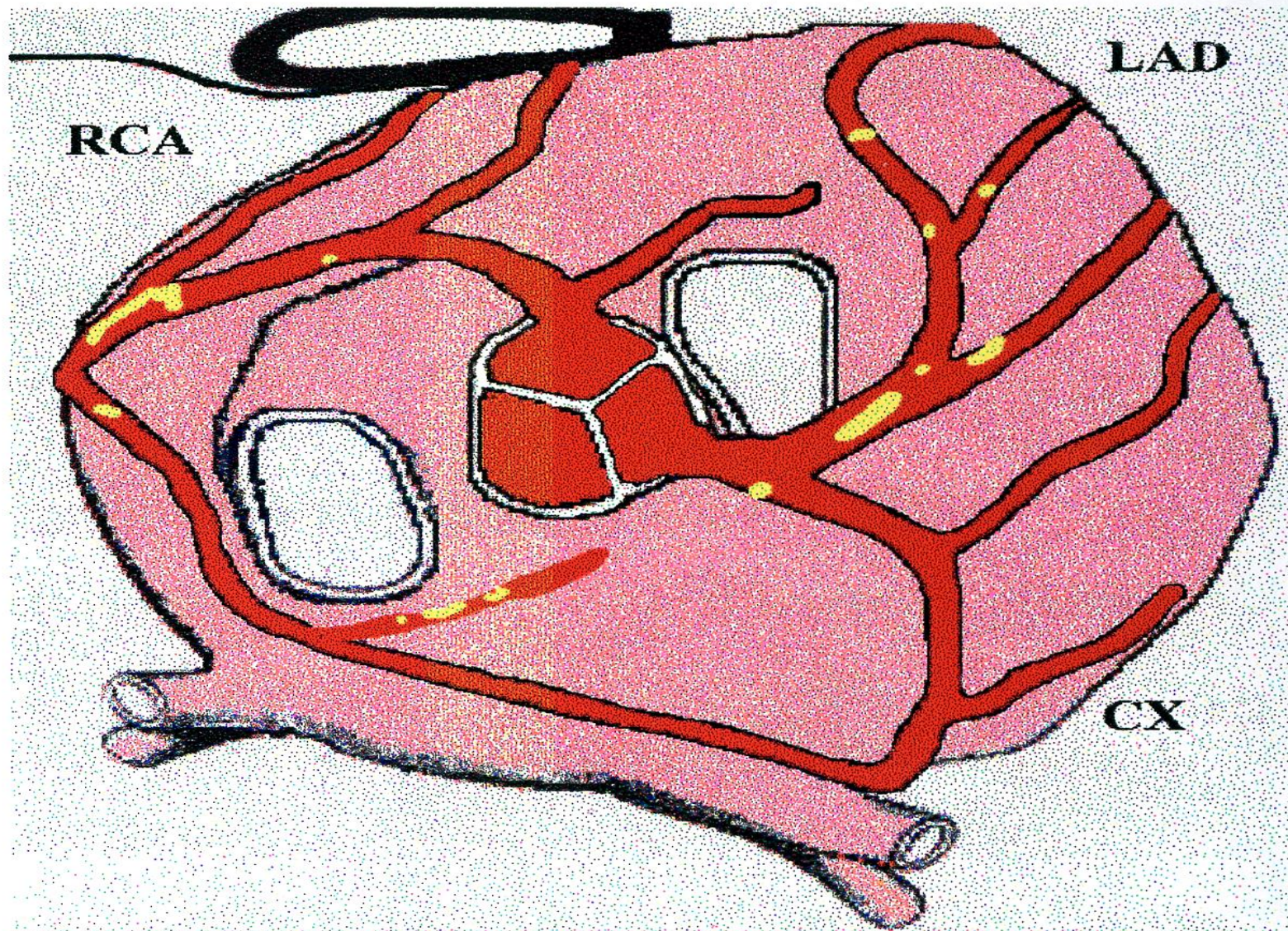
- Dysfunctional bioenergetics and energy starvation of myocardium requires metabolic support
- Two year multi-center randomized double-blind study – 420 patients
- All cause mortality lower in CoQ10 group – 18 patients vs 36 patients placebo group and ↓ hospital admissions in Q group
- Fewer adverse events in Q group vs placebo
- Conclusion – CoQ10 should be considered part of maintenance Rx of CHF

Ref: S.A. Mortensen, et al. The Effect of Coenzyme Q10 on Morbidity and Mortality in Chronic Heart Failure. Results from the Q-SYMBIO Study. Abstract 440. Heart Failure Association of the European Society of cardiology.

# 2013 – 5 Year Prospective Randomized Double-Blind Placebo- controlled Trial Among Elderly Swedish Citizens

- Selenium and CoQ10 essential to cells
- Low contents of selenium and Q10 shown in patients with cardiomyopathy
- 443 patients aged 70 to 88
- Selenium and CoQ10 vs placebo
- Significant reduction in mortality active group - 5.9% vs 12.6% control
- N-terminal pro-B-type natriuretic peptide (NT-proBNP) and echocardiographic measurement significant improvement





**Figure 1.** Axial view schematic of the heart



# Cardiac Transplantation

## *Coenzyme Q10*

### Major Improvement in Quality of Life Index

Reference:

Berman M., et al. Coenzyme Q10 in end-stage HF. *Clin. Cardiol.* 2004; 27,295-299

# Cardiac Transplantation and Coenzyme Q10

- 20,000 patients < 65 eligible
- Donors for only 10% of eligible candidates
- 11 transplant candidates treated with CoQ10
- All improved:
  - 3 – Class IV to Class I
  - 4 – Class IV to Class II
  - 2 – Class IV to Class III
- Q10 proved efficacy and safety
- Improves quality of life
- Increases waiting time for donor
- May be an alternative to cardiac transplantation

Reference: Folkers, K., Langsjoen, P., Langsjoen, P.H., Therapy with Coenzyme Q10 of patients in heart failure who are eligible or ineligible for a transplant, *Biochem Biophys Res Commun*, 1992;182 (1) : 247-53.

# Deficiency Signs and Symptoms

- Impaired CoQ10 synthesis – nutritional deficiency, genetic, or acquired defect in CoQ10 synthesis, pharmaceutical drugs
- Increased tissue needs - Heart in CHF
- Increased tissue levels – heart continuously aerobic – 10 times greater than other tissues in the body, including brain
- Aging – CoQ10 levels decline with age
- Heart biopsy specimens show major deficiency in Q10. Up to 75% when compared to normal hearts

# Coenzyme Q10 and Congestive Heart Failure

- 80 patients with CHF
- Double-blind study - 100 mg CoQ10 vs. placebo for three months with crossover design
- Improvements noted with CoQ10 were significant and more positive than those obtained from conventional drug therapy

Reference: Hoffman-Bang C, et al, CoQ10 as an Adjunctive Treatment of Congestive Heart Failure. Presented at the American College of Cardiology, 1992. Supplement 216A.

# Coenzyme Q10 and Congestive Heart Failure

- Double-blind study - 641 patients receiving Coenzyme Q10 2mg/kg or placebo for one year
- 20% reduction in hospitalizations in the CoQ10 group vs. placebo
- Lowers cost of medical care

Reference: Morisco et al., Effective CoQ10 Therapy in Patients With Congestive Heart Failure: a long-term multi-center randomized study. *Clinical Investigation* 71, 1993:134-136.

# Controlled Trials on Coenzyme Q10 1972-2015

*51- Some benefit*  
*4 - No benefit*

Last two negative trials, Australian and Maryland, well-designed but inadequate blood levels for biosensitive result

# Protection by Coenzyme Q10 From Myocardial Reperfusion Injury

- Forty patients randomized to placebo vs. 150mg of CoQ10 seven days before surgery
- Free radical indices, i.e., MDAs and conjugated dienes significantly lower in experimental group
- Treatment group showed significantly lower incidence of ventricular arrhythmias during recovery period
- Dosage of dopamine to maintain stable hemodynamics significantly lower in experimental group
- Findings suggest that CoQ10 plays a protective role in ischemic bypass by reducing degree of peroxidative damage

Reference: Cello, M et al. *Annals of Thoracic Surgery*, 1994:1427-32.

# Randomized, Double-Blind Placebo-Controlled Trial of Coenzyme Q10 in Patients with Acute Myocardial Infarction

120 mg of Hydrosoluble Q10 (73 pts) vs Placebo (71 pts)

Angina

Total arrhythmia

Compromised LV function

9.5% vs 25.3%

Total cardiac events  
including cardiac death  
and nonfatal infarction

15% vs 30.9%

Lipid peroxides, diene conjugates, and malondialdehyde

All significantly reduced in Q10 group

Conclusion: Coenzyme Q10 can provide rapid protective effects in patients with AMI if administered within 3 days of symptoms



# Potential Therapeutic Uses of Coenzyme Q10

- Unstable Angina Syndrome
- Myocardial Preserving Agent During Chemical Thrombolysis
- Angina Pectoris
- Myocardial Preserving Agent for Cardiac Surgery
- Congestive Heart Failure
- Toxin-Induced Cardiotoxicity (Adriamycin)
- Essential and Renovascular Hypertension, Renal Dysfunction
- Ventricular Arrhythmia
- Mitral Valve Prolapse - Magnesium
- Prevents Oxidation of LDL
- Diastolic Heart Failure

# Adverse Effects of Coenzyme Q10

- No serious toxicity has ever been associated with CoQ10
- Dosages in excess of 100 mg may cause mild insomnia
- Liver enzyme elevation has been detected in patients taking 300 mg or more per day but no liver toxicity reported
- Minor epigastric discomfort and diarrhea
- Other reported side effects include photophobia, irritability, and heartburn.
- Controversial relationship with the anticoagulant drug Warfarin
- Parkinson Study 1200 mg/day

# 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, Propionyl-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
- Diastolic Dysfunction (DD)

# L-carnitine and Angina

- 200 patients, 40 to 65, exercise-induced angina
- Usual drug Rx and 2 gms of L-carnitine or placebo
- Verum group - Significant reduction in ventricular ectopics, improved exercise tolerance, reduced ST segment response on exercise.

Reference: Cacciatore L et al. The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: A controlled study. *Drugs Exptl Clin Res* 1991;43:300-306.



# L-carnitine and Heart Attack

*Controlled study of 160 patients with MI*

- 80 received 4 gms of L-carnitine for 12 months
- 80 received placebo
- All on conventional Rx
- \*Mortality 1.2% on carnitine supplementation
- 12.5% controls

Reference: Davini P, et al: Controlled study on L-carnitine therapeutic efficacy in post-infarction. *Drugs Exp Clinic Res* 1992;18:355-365.

# A Randomized, Double-Blind, Placebo-Controlled Trial of L-carnitine in Suspected Acute Myocardial Infarction

*100 Patients - Suspected MI*

Verum - 2 gms L-carnitine - 28 days

Death rate: 15.6% carnitine group vs.  
26% placebo

# L-carnitine and Myocardial Infarction Studies

- Improvement in EF
- Limitation of infarct size
- Less CHF
- Improvement in arrhythmia
- Reduction in subsequent cardiac death

References: 1. Davini P et al.  
2. Singh RB et al.  
3. Iliceto S et al: Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: The L-carnitine Ecocardiografia Digitalizzata Infarto Miocarioco (CEDIM) Trial. *JACC* 1995;26(2):380-7.

# Mayo Clinic Review of 13 Clinical Studies on L-carnitine, April 2013

- 3629 patients with heart attack
- ↑ survival benefits of L-carnitine – limit infarct size, stabilize heart cell membranes and improve cellular energy metabolism
- Conclusion: ↓ in all cause death in large heart group 27%, ↓ anginal symptoms 40%, ↓ ventricular arrhythmias 65%

Ref: J.D. DiNicolantonio, et al. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. May Clinic Proceed. 88(6), 544-551(2013).

# Carnitine and 100 year olds+

- 66 men & women 100 and older
- Six months – 1 group 2 grams of L-carnitine; 1 group placebo
- Carnitine laced Centenarians ↑ in energy, mental function, muscle mass; ↓ fat mass and ↓ fatigue
- Major improvement in sarcopenia (loss of muscle);  
↑ 8 lbs muscle, ↓ 4 lbs fat

Ref: Malaguarnera M, et al. L-carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. Am J Clin Nutr, 2007;86(6):1738-44.

# 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 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.”

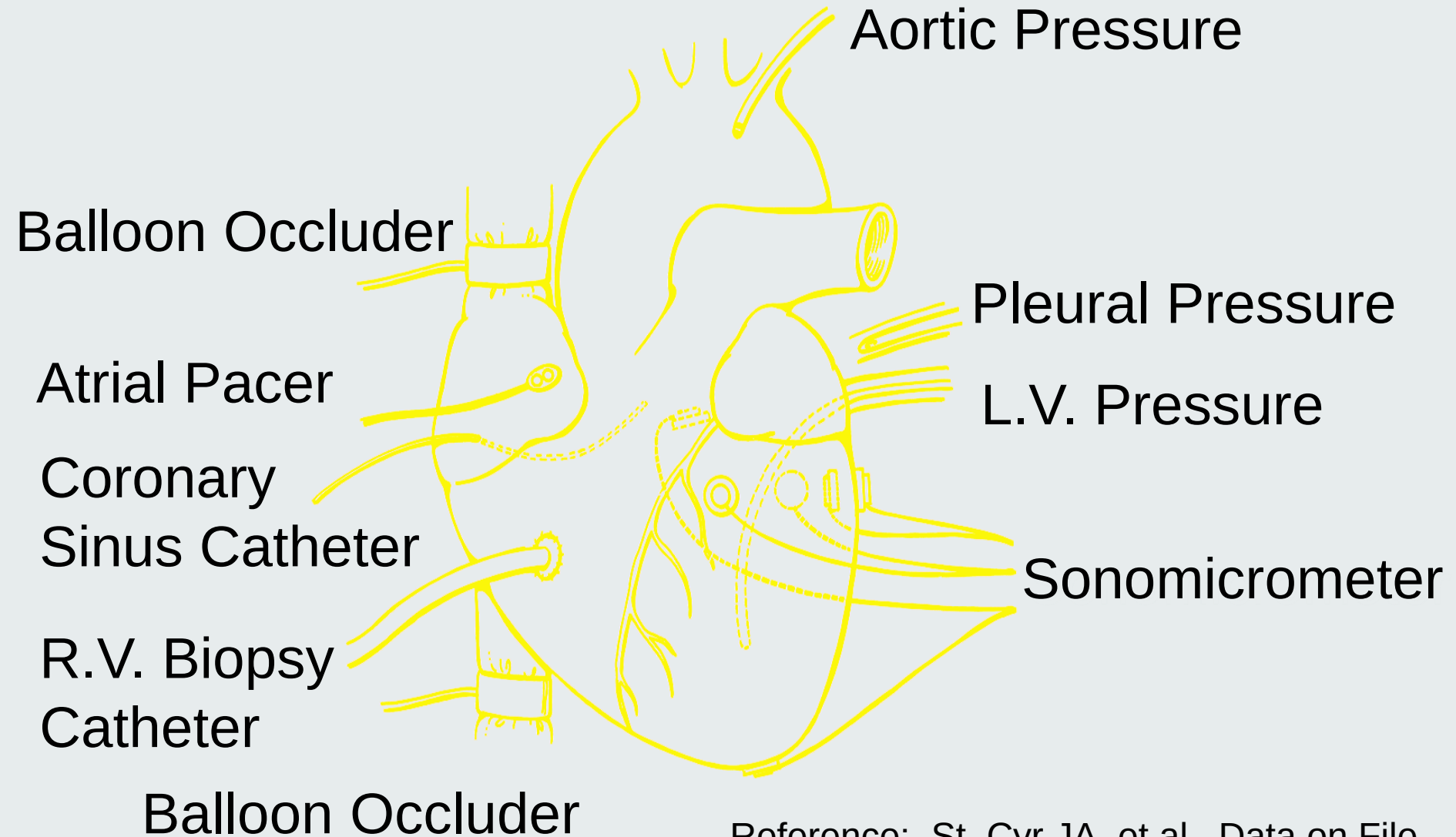
# D-ribose

- 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

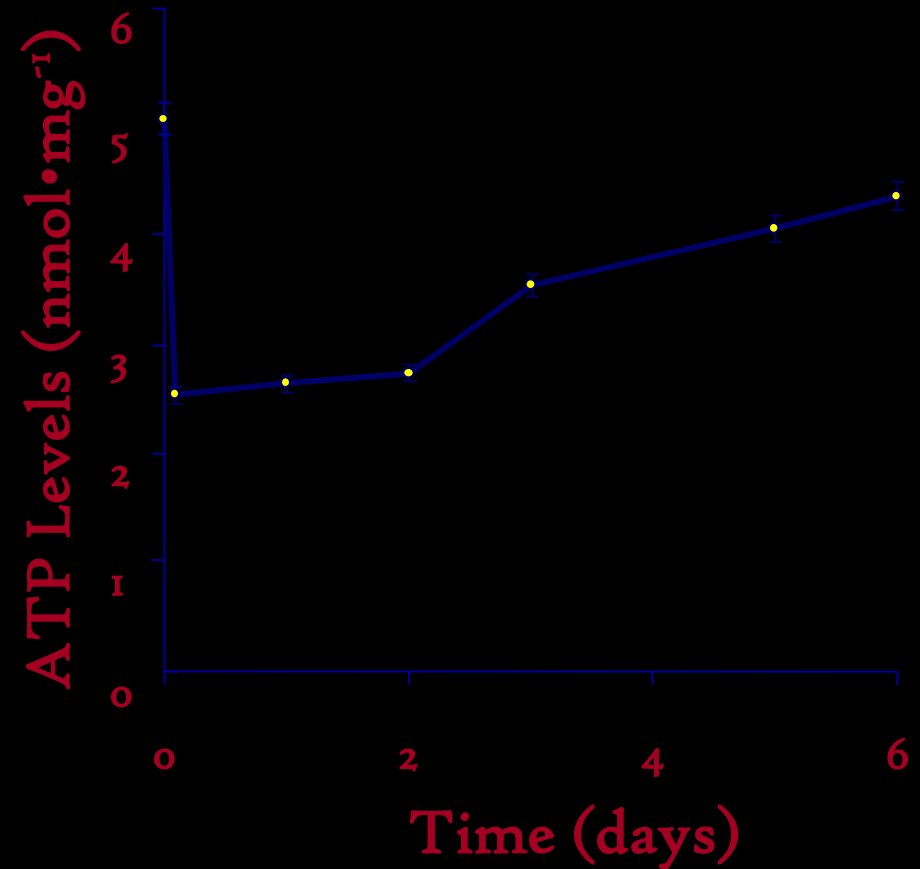
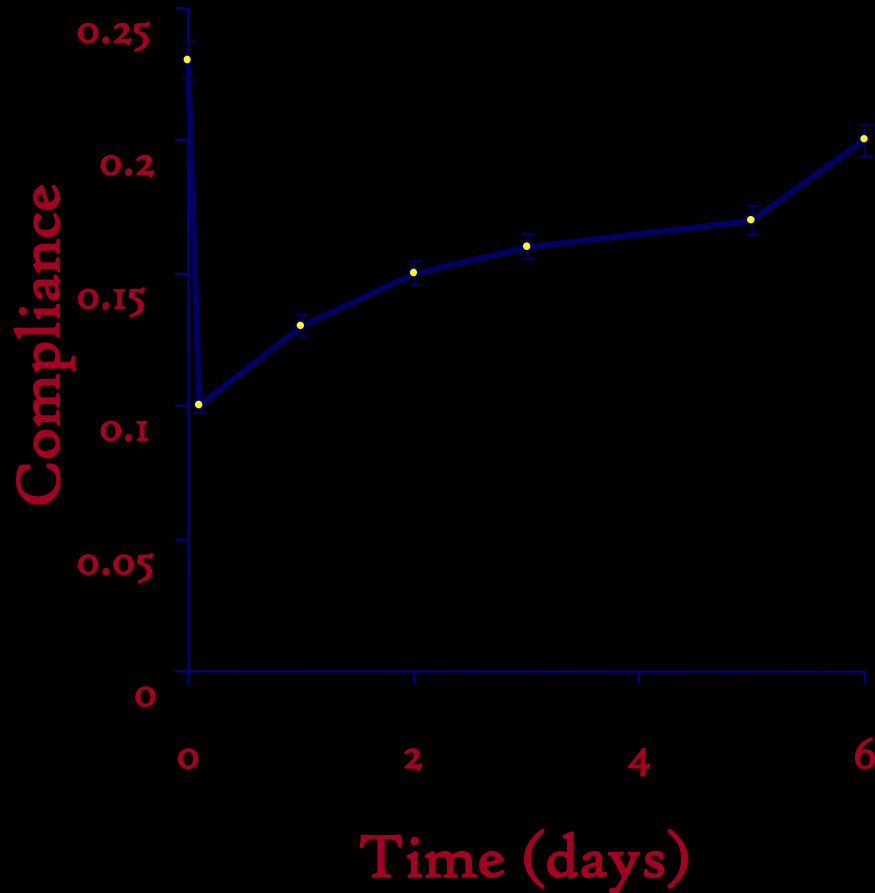


Reference: St. Cyr JA, et al. Data on File.

## LV Compliance

## Myocardial ATP Levels

Following Global Ischemia



# Correlation Between ATP Level and Diastolic Function

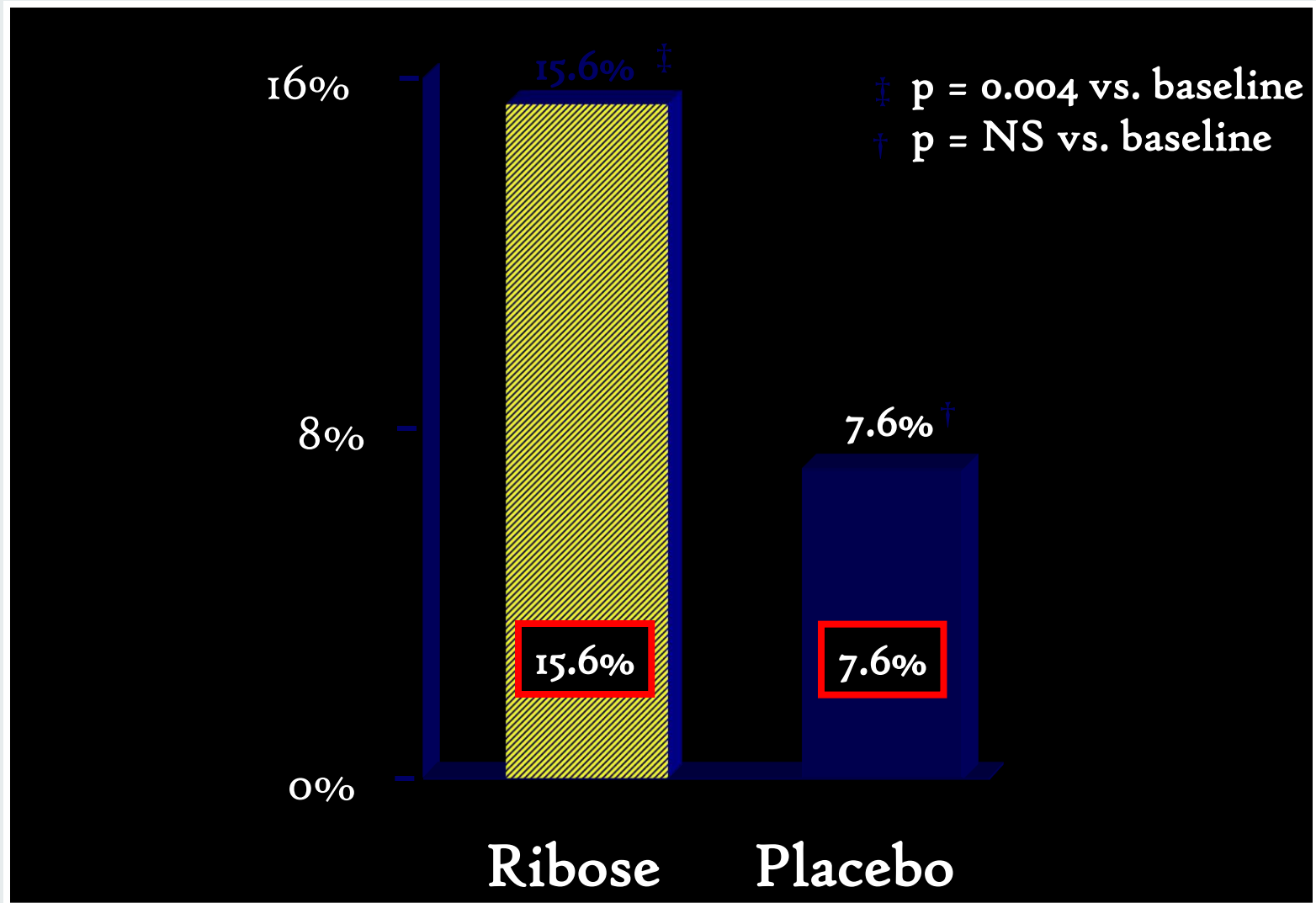
- Ischemia - dramatic drop in ATP concentration
- Decreased ATP corresponds to loss of diastolic function
- Administration of D-ribose – improvement in diastolic function

# Ribose in Exercise Induced Ischemia

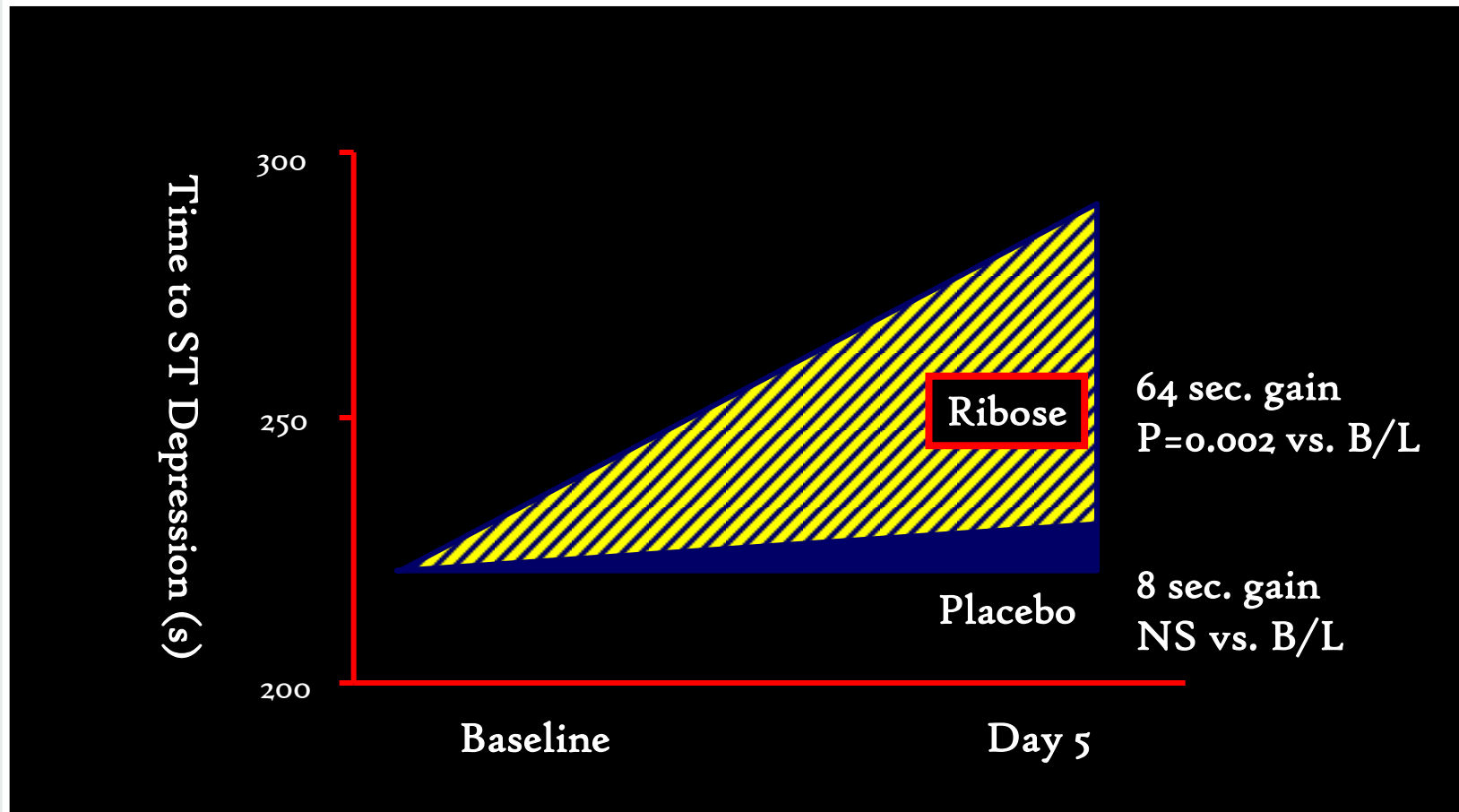
- 20 male subjects with stable, but severe, CADz
  - $\geq 1$  mm ST-segment depression & angina within 9:00 minutes
  - $\geq 75\%$  narrowing in at least one vessel
- Maximal stress EKG on day 1; repeat on day 2
- Randomized to receive 3 days of
  - Ribose, 15 gm qid
  - Placebo (dextrose), 15 gm qid
- Maximal stress test EKG on day 5
- Double blind protocol followed

Reference: Pliml, et al. The Lancet 340(8818):507-510, 1992.

# Change in Time to Moderate Angina



# Time to ST-Segment Depression

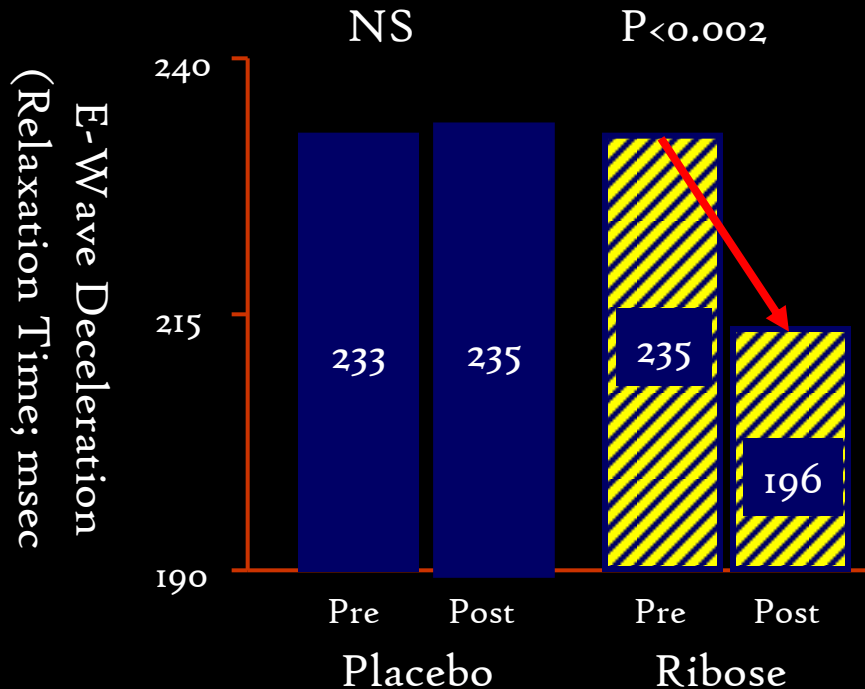


# Ribose in Congestive Heart Failure

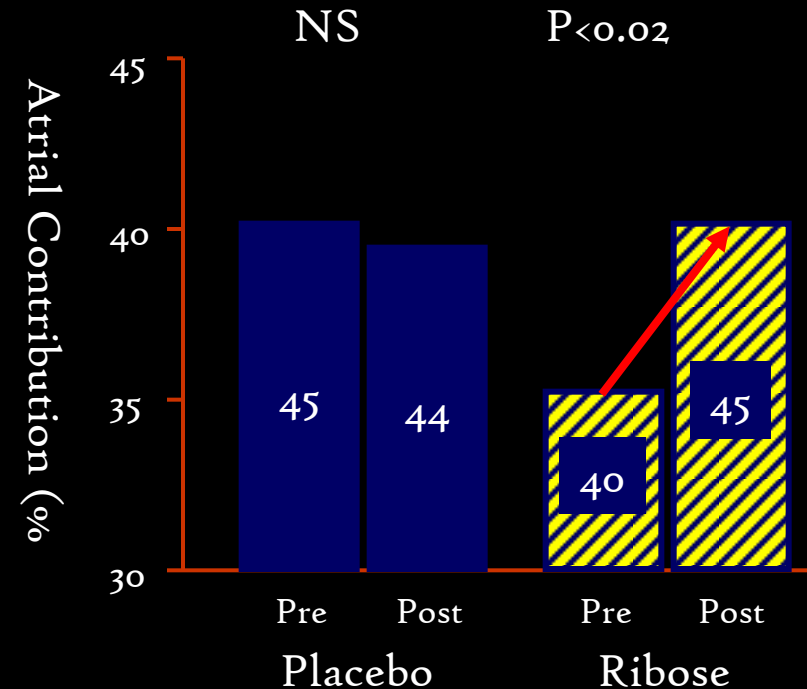
- 15 subjects; (NYHA II or III) ischemic cardiomyopathy
  - 2/3 with 3V Dz; mean ejection fraction 47% (range 28% - 71%)
- Randomized to receive over 3 weeks
  - Ribose; 5 gm tid
  - Placebo (dextrose); 5 gm tid
- Pre- and post-treatment measure
  - ECHO measures of diastolic and systolic function
  - Physical performance (exercise tolerance)
  - Quality of life (SF-36 score)
- Cross over to alternative treatment after one week washout period
- Double blind protocol followed

# Echo Measures of Diastolic Function

## E-Wave Deceleration Time



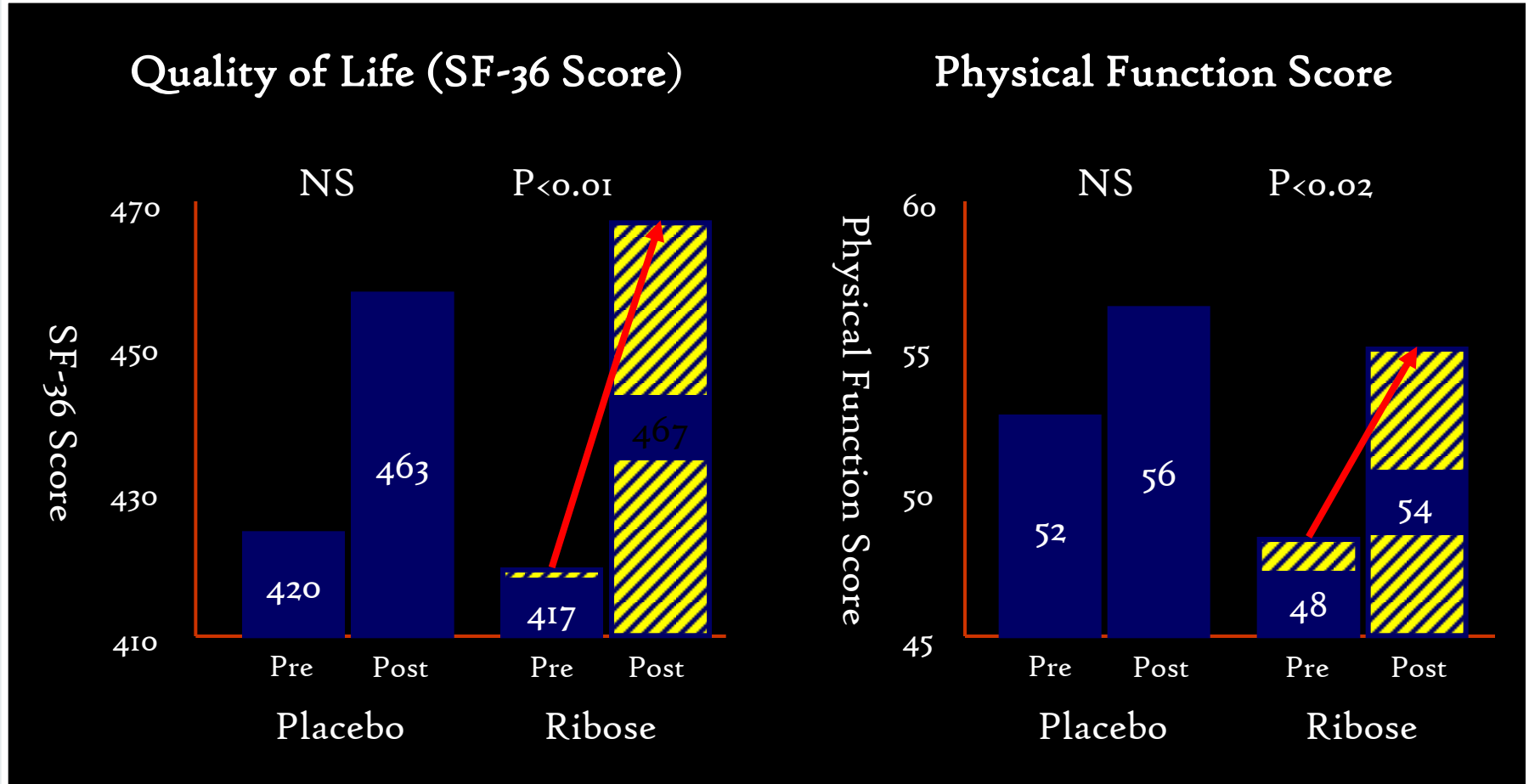
## Atrial Contribution to LV Filling



*Faster deceleration, enhanced atrial contribution = greater ventricular compliance*



# Quality of Life Measures



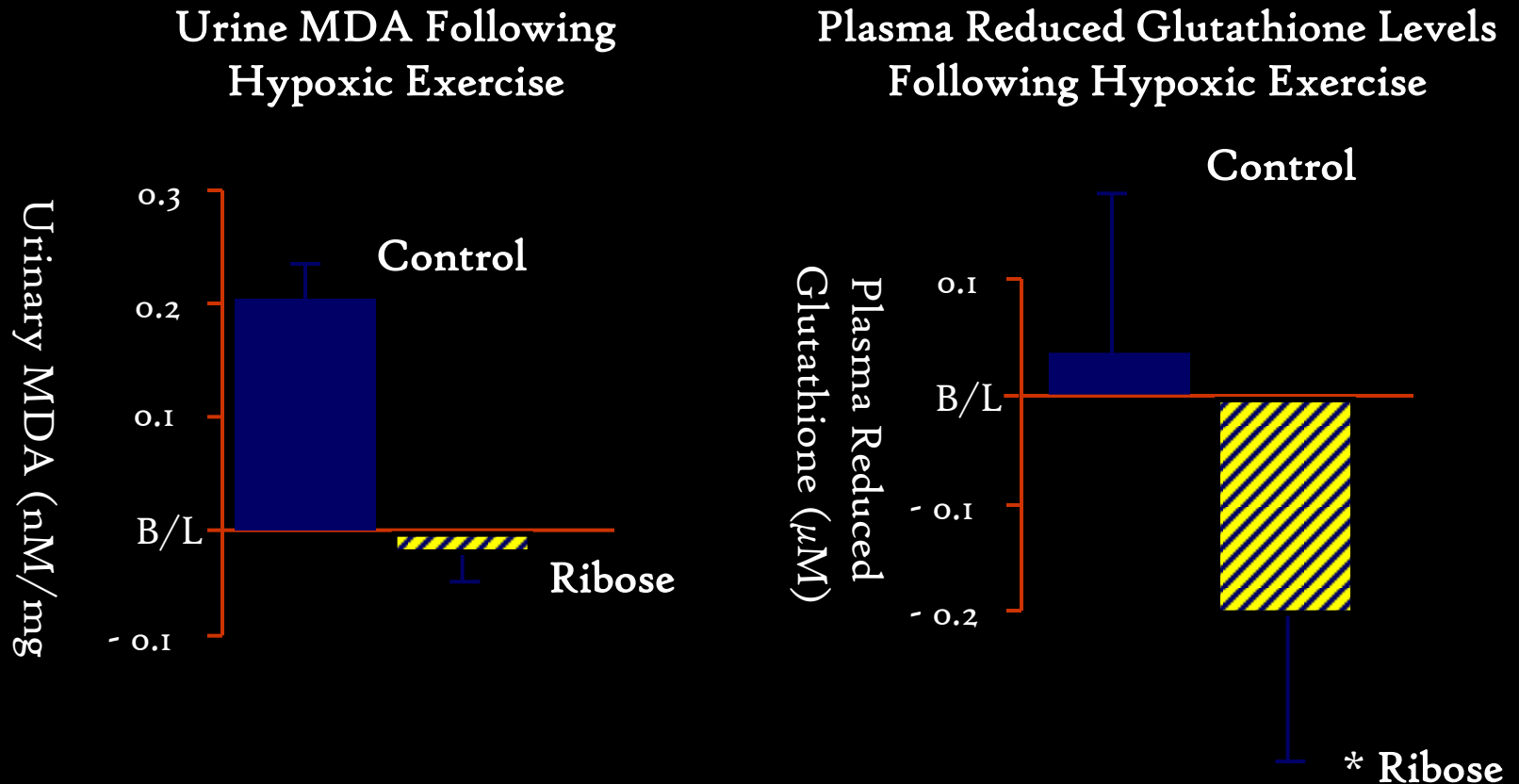
*Enhanced quality of life and exercise tolerance*

# Ribose in Athletic Performance

## Free Radical Formation & Cardiac Stress

- 7 health volunteers
- Drink 250 cc water pre- and post-exercise randomized to contain
  - Ribose; 7-gm
  - Placebo (dextrose); 7-gm
- Cycle at lactic acid threshold X 25"; breathing air 16% O<sub>2</sub>
  - Measure heart rate
- Rest X 60" breathing room air, the measure
  - Urine malondialdehyde (MDA)
  - Plasma reduced glutathione (GSH)
- Repeat with alternate drink after one week washout
- Double blind protocol followed (crossover design)

# Free Radical Formation & Glutathione Depletion



Significant increase/decrease over pre-exercise levels.

# Conclusions

- Ribose (the critical precursor) enhances recovery of both myocardial ATP levels and diastolic function
- ATP recovery is enhanced by ribose infusion as late as 72 hours post ischemia
- No matter whether ATP levels increase or decrease, diastolic functional changes follow the increase or decrease

Therefore...

Post-ischemic function is related to [ATP]

# Documented Benefits of D-ribose

- Improves treadmill findings in patients with CAD
- Better diastolic function, QOL, and functional status in CHF
- Accelerates recovery of systolic function post CABG
- Speeds recovery of muscle ATP following anaerobic exercise
- Enhances strength and endurance gain with weight training
- Decreases free radical stress during anaerobic exercise
- Benefit in fibromyalgia

# Summary

## Cardiovascular Indications

### CoQ10 and Carnitine

- Arrhythmia
- Angina
- Heart Failure
- Claudication
- Raising HDL
- Lowering LDL, LP(a)
- Blood Pressure lowering

### D-Ribose

- Arrhythmia
- Angina
- Heart Failure
- Peripheral Vascular Disease
- Statin-induced myalgia
- Ischemic muscle tissue

# 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



Metabolic Cardiologist's  
approach to aging,  
strenuous exercise and  
cardiac pathology,  
fibromyalgia and  
metabolic syndrome

# Age Management Program

- For patients looking for a simple age-management program and interested in cardiovascular prevention at the same time, my daily dosage recommendations are as follows:
  - Multivitamin/mineral foundation program with 1 gm of fish oil
  - Coenzyme Q10: 90-150 mg
  - L-carnitine: 500-1000 mg
  - D-ribose: 5 gm
  - Magnesium: 400 mg

# High Blood Pressure

- Multivitamin/mineral foundation program with 1 gm of fish oil
- Coenzyme Q10: 180-360 mg
- L-carnitine: 500-1000 mg
- D-ribose: 5-10 grams
- Magnesium: 400-800 mg
- Additional Fish Oil: 2 grams
- Garlic: 1 gram
- Hawthorne Berry: 1000-1500 mg

Please note: Garlic and Hawthorne berry have very similar action to ACE (angiotensin converting enzyme) inhibitors in lowering blood pressure.

# Angina Pectoris

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 180-360 mg
- L-carnitine: 1000-2000 mg
- D-ribose: 10-15 grams
- Magnesium: 400-800 mg

Note: I also recommend a daily beverage of green tea for any of my patients suffering from angina pectoris. In one Japanese study including over 500 men with documented coronary artery disease, the only beverage that seemed to prevent heart attack was one daily cup of green tea per day.

# Cardiac Arrhythmia-Prevention of Premature Ventricular Contractions, Premature Atrial Contractions, and Intermittent Atrial Fibrillation

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 180-360 mg
- L-Carnitine: 1000-2000 mg
- D-ribose: 5-10 grams
- Magnesium: 400-800 mg
- Additional Fish Oil: 2-3 grams

Note: Increase fish oil to at least 3 to 4 grams daily. Fish oil has a positive effect on heart rate variability and supports “calming” of the heart. Considerable research has suggested that fish oil prevents cardiac arrhythmia, which can be a precursor to malignant arrhythmias and even sudden cardiac death.

# Congestive Heart Failure

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 300-360 mg daily
- L-carnitine: 2000-2500 mg daily
- D-ribose: 10-15 grams
- Magnesium: 400-800 mg

# Severe Congestive Heart Failure, Dilated Cardiomyopathy, Patients Awaiting Heart Transplantation

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 360-600 mg
- L-carnitine: 2500-3500 mg
- D-ribose: 15 grams
- Magnesium: 400-800 mg

Note: If quality of life is still not satisfactory, add 1500 mg of Hawthorne Berry and 2-3 grams of taurine, as the addition of these two nutraceuticals has helped many of my patients with severe refractory congestive heart failure.

# Mitral Valve Prolapse

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 90-150 mg daily
- L-carnitine: 500-1000 mg daily
- D-ribose: 5 grams
- Magnesium: 800 mg

Note: If the mitral valve prolapse symptoms are accompanied by frequent arrhythmia, then the addition of 3 grams of fish oil is suggested.



# Fibromyalgia, Chronic Fatigue Syndrome, or Mitochondrial Cytopathies

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 300-360 mg
- L-carnitine: 2000-3000 mg
- D-ribose: 15 grams
- Magnesium: 400-800 mg

# Syndrome X, Insulin Resistance, and Type 2 Diabetes

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 180-360 mg
- L-carnitine: 1000-2000 mg
- D-ribose: 5 grams
- Magnesium: 800 mg

Note: There are also many nutraceuticals you can take for the regulation of glucose metabolism. I like alpha lipoic acid in doses of 100-400 mg, gymnemma sylvestre in doses of 50-100 mg, and 1 mg of vanadyl sulphate daily. In addition, there is new and exciting research regarding the use of cinnamon. Whenever you are battling type 2 diabetes, insulin resistance, or Syndrome X, it is absolutely necessary to maintain a low glycemic load carbohydrate diet, with no more than 40 percent of the calories coming from preferably low glycemic load carbohydrates. The monounsaturated fats and polyunsaturated fatty acids such as alpha linolenic acid and other Omega 3 fatty acids in addition to higher dose proteins do not require a significant insulin release for metabolism.

# A Program for Professional or World Class Athletes

- Multivitamin/mineral foundation program with 1 gram of fish oil
- Coenzyme Q10: 300-360 mg
- L-carnitine: 2000-3000 mg
- D-ribose: 15-20 grams
- Magnesium: 800 mg

Note: Most athletes are also deficient in vitamin E and an additional 400-800 units is recommended. Most female athletes are also deficient in iron and an additional 18-36 mg is recommended for menstruating world-class athletes.

# References

- Chopra RK, Goldman R, Sinatra ST, Bhagavan HN. Relative bioavailability of coenzyme Q10 formulations in human subjects. *Int J Vitam Nutr Res*. 1998;68(2):109-13.
- Berman M, A Erman, T Ben-Gal, et al. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: A randomized, placebo-controlled study. *Clin Cardiol* 2004;27:295-299.
- Geleijnse JM, Vermeer C, Grobbee DE, et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam study. *J Nutr*. 2004;134(11):3100-3105.
- Kaneki M, Hosoi T, Ouchi Y, et al. Pleiotropic actions of vitamin K: protector of bone health and beyond? *Nutrition*. 2006;22(7-8):845-852.
- Kidd PM, et al. Coenzyme Q10: Essential energy carrier and antioxidant. *HK Biomed Consult* 1998;1-8.
- Stanley WC, Hoppel CL. Mitochondrial dysfunction in heart failure: Potential for therapeutic interventions? *Cardiovasc Res* 2000;45:805-806.
- Bayeva M, Gheorghiade M, Arhdehali H. Mitochondria as a therapeutic target in heart failure. *J Am Coll Cardiol* 2013;61(6):599-610.

# References continued

- Luo G, Ducy P, McKee M, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature*. 1997;386:78-81.
- Omran H, D MacCarter, JA St. Cyr, B Luderitz. D-Ribose aids congestive heart failure patients. *Exp Clin Cardiol* 2004;9(2):117-118.
- Omran H, et al. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: A prospective feasibility study. *Eur J Heart Failure* 2003;5:615-619.
- Pauly D, C Johnson, JA St. Cyr. The benefits of ribose in cardiovascular disease. *Med Hypoth* 2003;60(2):149-151.
- Pauly D, C Pepine. D-Ribose as a supplement for cardiac energy metabolism. *J Cardiovasc Pharmacol Ther* 2000;5(4):249-258.
- Schurgers LJ, Aebert H, Vermeer C, et al. Oral anticoagulant treatment: friend or foe in cardiovascular disease? *Blood*. 2004;104(10):3231-3232.
- Schurgers LJ, et al. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. *Blood*. 2006 Nov; [Epub ahead of print].
- Schurgers LJ, et al. Vitamin K-containing dietary supplements: comparison of synthetic vitamin K1 and natto-derived menaquinone-7. *Blood*. 2006 Dec; [Epub ahead of print].

# References continued

- Sinatra ST. Coenzyme Q10 and congestive heart failure. *Ann Intern Med*. 2000 Nov 7;133(9):745-6.
- Sinatra ST. Coenzyme Q10: a vital therapeutic nutrient for the heart with special application in congestive heart failure. *Conn Med*. 1997 Nov;61(11):707-11.
- Sinatra ST. Refractory congestive heart failure successfully managed with high dose coenzyme Q10 administration. *Mol Aspects Med*. 1997;18 Suppl:S299-305.
- Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science* 2009;324:98-102.
- Parmacek MS, Epstein JA. Cardiomyocyte renewal. *N Engl J Med* 2009;361;1:86-88.
- Neubauer S. The failing heart: An engine out of fuel. *N Engl J Med* 2007;356(11):1140-1151.
- Sinatra ST. *The Sinatra Solution/Metabolic Cardiology*. Laguna Beach, CA: Basic Health Publications, 2005.

# References continued

- Singh RB, et al. Effect of coenzyme Q10 on risk of atherosclerosis in patients with myocardial infarction. *Mol Cell Biochem* 2003; 246:75-82.
- Zimmer HG. Regulation of and intervention into the oxidative pentose phosphate pathway and adenine nucleotide metabolism in the heart. *Mol Cell Biochem* 1996;160-161:101-109.
- Ingwall JS, Weiss RG. Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circ Res.* 2004;95(2):135-45.
- Khan NA, Daskalopoulou SS, Karp I, et al. GENESIS PRAXY Team. Sex differences in acute coronary syndrome symptom presentation in young patients. *JAMA Intern Med* 2013;173(20):1863-1871.
- Engberding N, Wenger NK. Management of Hypertension in Women. *Hypertension Research* 2012;35:251-260.
- Kaneki M, Hosoi T, Ouchi Y, et al. Pleiotropic actions of vitamin K: protector of bone health and beyond? *Nutrition.* 2006;22(7-8):845-852.
- Koos R, Mahnken AH, Muehlenbruch G, et al. Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computer tomography. *Am J Cardiol.* 2005;96(6):747-749.

# References continued

- Wassertheil-Smoller S, Anderson G, Psaty BM, et al. Hypertension and its treatment in postmenopausal women: Baseline data from the Women's Health Initiative. *Hypertension* 2000;36:780-789.
- “Medical researchers have found that birth control pills increase blood pressure in some women” and “According to the National Heart, Lung, and Blood Institute (NHLBI), high blood pressure affects 6-8 percent of all pregnancies in the United States.” – The American Heart Association (AHA). High Blood Pressure and Women. Heartorg accessed June 24, 2014.
- Luo G, Ducky P, McKee M, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature*. 1997;386:78-81.
- Sinatra ST, Roberts JC. *Reverse Heart Disease Now*. Hoboken, NJ: John Wiley, 2007.
- Tanaka J, Tominaga R, Yoshitoshi, et al. Coenzyme Q10: The prophylactic effect on low cardiac output following cardiac valve replacement. *Ann Thorac Surg* 1982;33:145-151.
- Sinatra ST. Letter to the Editor: Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: A randomized, placebo-controlled study. *Clin Cardiol* 2004;27(10):A26.



# References continued

- Forman JP, Stampfer MJ, Curhan GC. Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension* 2005;46(3):500-507.
- Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260-269.
- Schurgers LJ, Teunissen K, Knapen M, et al. Novel conformation-specific antibodies against matrix  $\gamma$ -carboxyglutamic acid (GLA) protein: undercarboxylated matrix GLA protein as a marker for vascular calcification. *Arterioscler Thromb Vasc Biol.* 2005;25(8):1629-1633.
- Lazon J, Pomeranz B, Corey P. Incidence of adverse drug reaction in hospitalized patients. *JAMA* 1998;279:1200-1205.
- Watson PS, Scalia GM, Gaibraith AJ, et al. Is coenzyme Q10 helpful for patients with idiopathic cardiomyopathy? *Med J Aust* 2001;175(8):447, author reply 447-448.
- Khatta M, Alexander BS, Krichten CM, et al. The effect of coenzyme Q10 in patients with congestive heart failure. *Ann Intern Med* 2000;132(8):636-640.
- Narin F, Narin N, Andac H, et al. Carnitine levels in patients with chronic rheumatoid heart disease. *Clin Biochem* 1997;30(8):643-645.

# References continued

- Singh RB, et al. A randomized, double-blind, placebo-controlled trial of L-carnitine in suspected myocardial infarction. *Postgrad Med* 1996;72:45-50.
- Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*;2006;355:251-259.
- Yancy CW, Lupo M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: A report from the acute decompensated heart failure national registry (adhere) database. *J Am Coll Cardiol* 2006;47:76-84.
- Mortensen SA, Kumar A, Dolliner P, et al. The effect of Coenzyme Q10 on morbidity and mortality in chronic heart failure. Results from Q-SYMBIO study. Presented at Heart Failure Congress 2013 Final Programme Number 440, Coenzyme Q10 as adjunctive treatment of chronic heart failure: A randomized double blind multicenter trial with focus on changes in symptoms, biomarker status with BNP and long term outcome. *JACC Heart Fail* 2014 Sep 25. p.ii: S2213-1779(14)00336-9.

# References continued

- Bashore TM, et al. Histologic and biochemical correlates of left ventricular chamber dynamics in man. *J Am Coll Cardiol* 1987;9:734-42.
- Bresolin N, Martineeli P, Barbiroli B, et al. Muscle mitochondrial DNA deletion and <sup>31</sup>P-NMR spectroscopy alterations in a migraine patient. *J Neurol* 1991;104:182-189.
- Buhaescu I, Izzedine H. Mevalonate pathway: a review of clinical and therapeutical implications. *Clin Biochem* 2007 Jun; 40(9-10):575-84.
- De Pinieux G, Chariot P, Ammi-Said M, et al. Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. *Br J Clin Pharmacol* 1996; 42(3):333-7.
- Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008;8(6):373-418.

# References continued

- Greenwood SM, Connolly CN. Dendritic and mitochondrial changes during glutamate excitotoxicity. *Neuropharmacology* 2007 Dec;53(8):891-898. Epub 2007 Oct 14.
- Halley CM, et al. Mortality rate in patients with diastolic dysfunction and normal systolic function. *Arch Intern Med* 2011;171(12):1082-87.
- Ingwall JS. *ATP and the Heart*. Kluwer Academic Publishers: Boston, 2002.
- Koo B, Becker LE, Chuang S, et al. Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS): clinical, radiological, pathological, and genetic observations. *Ann Neurol* 1993; 34:25-32.
- Lanteri-Minet M, Desnuelle C. Migraine and mitochondrial dysfunction. *Rev Neurol* 1996;152:234-238.
- Mahoney DJ, Parise G, Tarnopolsky MA. Nutritional and exercise-based therapies in the treatment of mitochondrial disease. *Curr Opin Clin Nutr Metab Care* 2002 Nov; 5(6):619-29.
- Montagna P, Cortell P, Barbiroli B. Magnetic resonance spectroscopy studies in migraine. *Cephalalgia* 1994;14:184-193.

# References continued

- Pina IL. Comment. *Arch Intern Med* 2011;171(12):1088-89.
- Redfield MM, SJ Jacobson, JC Burnett, DW Mahoney, KR Bailey, RJ Rodenheffer. Burden of systolic and diastolic ventricular dysfunction in the community. Appreciating the scope of the heart failure epidemic. *JAMA* 2003;289(2):194-202.
- Rundek T, Naini A, Sacco R, et al. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. *Arch Neurol* 2004 Jun;61(6):889-92.
- Schoenen J, Lenaerts M, Bastings E. High dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. *Cephalalgia* 1994;14:328-329.
- Sinatra ST. Metabolic Cardiology: the missing link in cardiovascular disease. *Altern Ther Health Med* 2009;15(2):48-50.
- Hunt SA, Abraham WT, Chin MH, et al. 2009 focused updated incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults a report of the American College of Cardiology foundation/American heart association task force on practice guidelines developed in collaboration with the international society for heart and lung transplantation. *J Am Coll Cardiol* 2009;53:e1-e90.

# References continued

- Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: An inconvenient truth! *J Am Coll Cardiol* 2010;55:526-537.
- Redfield MM, Jacobsen SJ, Burnett JC Jr, et al. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. *JAMA* 2003;289(2):194-202.
- Wenger NK, Hayes SN, Pepine CJ, et al. Cardiovascular care for women: The 10-Q report and beyond. *Am J Cardiol* 2013 Aug 15;112(4):S2.
- Alehagen U, Johansson P, Bjornstedt M, et al. Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. *Int J Cardiol* 2013;167(5):1860-1866.
- El-Aroussy W, Rizk A, Mayhoub G, et al. Plasma carnitine levels as a marker of impaired left ventricular functions. *Mol Cell Biochem* 2000;213(1-2):37-41.

# References continued

- Dai Y, Luk T, Yiu K, et al. Reversal of mitochondrial dysfunction by coenzyme Q10 supplement improves endothelial function in patients with ischemic left ventricular systolic dysfunction: A randomized controlled trial. *Atherosclerosis* 2011;216:395-401.
- Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306(8):856-863.
- Melduni RM, Suri RM, Seward JB, et al. Diastolic dysfunction in patients undergoing cardiac surgery: A pathological mechanism underlying the initiation of new-onset post-operative atrial fibrillation. *J Am Coll Cardiol* 2011;58:953-961.
- Jeresaty R. Mitral Valve Prolapse. New York, NY: Raven Press, 1979.
- ZuWallack R, Sinatra S, Lahiri B, et al. Pulmonary function studies in patients with prolapse of the mitral valve. *Chest* 1979;76(1):17-20.
- Halley CM, Houghtaling PL, Khalil MK, et al. Mortality rate in patients with diastolic dysfunction and normal systolic function. *Arch Intern Med* 2011;171(2):1082-1087.

# References continued

- Kitlinski M, Stepniewski M, Nessler J, et al. Is magnesium deficit in lymphocytes a part of the mitral valve prolapse syndrome? *Magnes Res* 2004;17(1):39-45.
- Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. *Lancet* 2013;382(9901):1329-1340.
- Hirsch AT, Allison MA, Gomes MS, et al. A call to action: Women and peripheral artery disease: A scientific statement from the American Heart Association. *Circulation* 2012;125(11):1449-1472.
- Chevalier G, Sinatra ST, Oschman JL, et al. Earthing (grounding) the human body reduces blood viscosity: A major factor in cardiovascular disease. *J Altern Complement Med* 2013;19(2):102-10.
- Chevalier G, Sinatra ST. Emotional stress, heart rate variability, grounding, and improved autonomic tone: Clinical applications. *Integr Med: A Clin J* 2011;10(3):16-21.



# References continued

- Ueland T, Svardal A, Oie E, et al. Disturbed carnitine regulation in chronic heart failure: increased plasma levels of palmitoyl-carnitine are associated with poor prognosis. *Int J Cardiol* 2013;167(5):1892-1899.
- Serati AR, Motamedi MR, Emami S, et al. L-carnitine treatment in patients with mild diastolic heart failure is associated with improvement in diastolic function and symptoms. *Cardiology* 2010;116:178-182.
- DiNicolantonio JD. L-carnitine in the secondary prevention of cardiovascular disease: systemic review and meta-analysis. *Mayo Clinic Proceed* 2013;88(6):544-551.
- Schimatschek HF, Rempis R. Prevalence of hypomagnesemia in an unselected German population of 16,000 individuals. *Magnes Res* 2001;14(4):283-290.
- Baliga RR, Young JB. Energizing diastole. *Heart Fail Clin* 2008;4(1):9-13.
- Schwartz K, Siddiqi N, Singh S, et al. The breathing heart: Mitochondrial respiratory chain dysfunction in cardiac disease. *Int J Cardiol* 2014;171(2):134-143.