Metabolic Cardiology

The Emerging New Frontier in the RX of CHF and CV Disease

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Learning Objectives

- Define the complex role of energy and the heart
- Learn how targeted nutraceuticals can help people survive heart disease and “buy time” for intrinsic stem cell renewal
- Discover the new triad of bioenergetic energy in supporting diastolic dysfunction – Coenzyme Q10, D-ribose and L-carnitine

Greatest Discoveries 40+ Years Cardiology

- CoEnzyme Q10 and Grounding – electron donors – origin of Vibrational Medicine
- CoQ10 and Grounding drive ATP in preferential direction and support blood thinning
- Blood viscosity must be considered in the computerized age of hypercoagulable blood
- Metabolic Cardiology – an opportunity for stem cell renewal??

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 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.

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.

New Clues in the Mystery of Heart Muscle Renewal

- Cardiomyocyte renewal (CR) & the Cold War
- Myocardium 40% regeneration after decades
- Can metabolic cardiology “Buy” time for CR?

Reference:

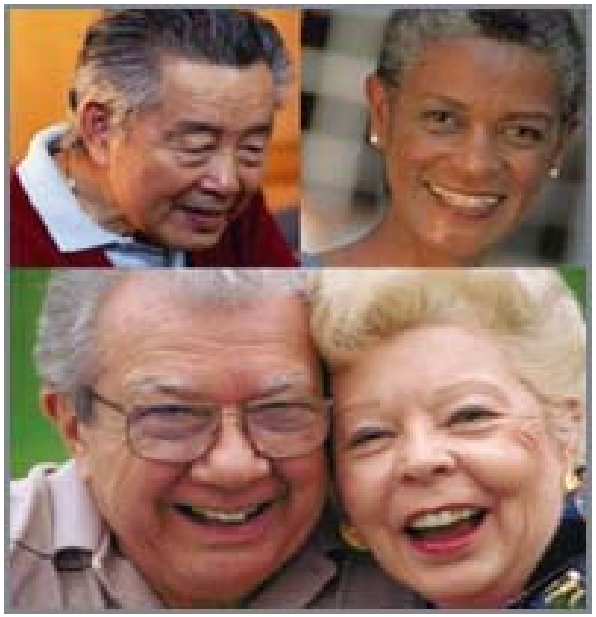
Bergmann O, Frisen J, et al. Evidence for cardiomyocyte renewal in humans. Science 2009;361(1):86-88.

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

Jim

Louise

Tommy



Helen

George

Catherine

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Dating the Heart: Exploring Cardiomyocyte Renewal in Humans

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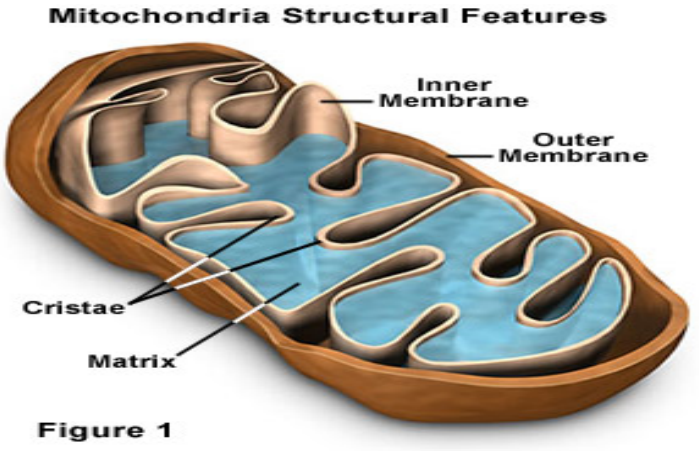
Regenerative mechanisms reported in the hearts of lower vertebrates have been recapitulated in the mammalian milieu, and recent studies have provided strong evidence for cardiomyocyte turnover in humans. These findings speak to an emerging consensus that adult mammalian cardiomyocytes do have the ability to divide, and it stands to reason that enrichment of this innate proliferative capacity should prove essential for complete cardiac regeneration.

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 – unlike nuclear DNA, defensive mechanisms are just emerging in current medical literature

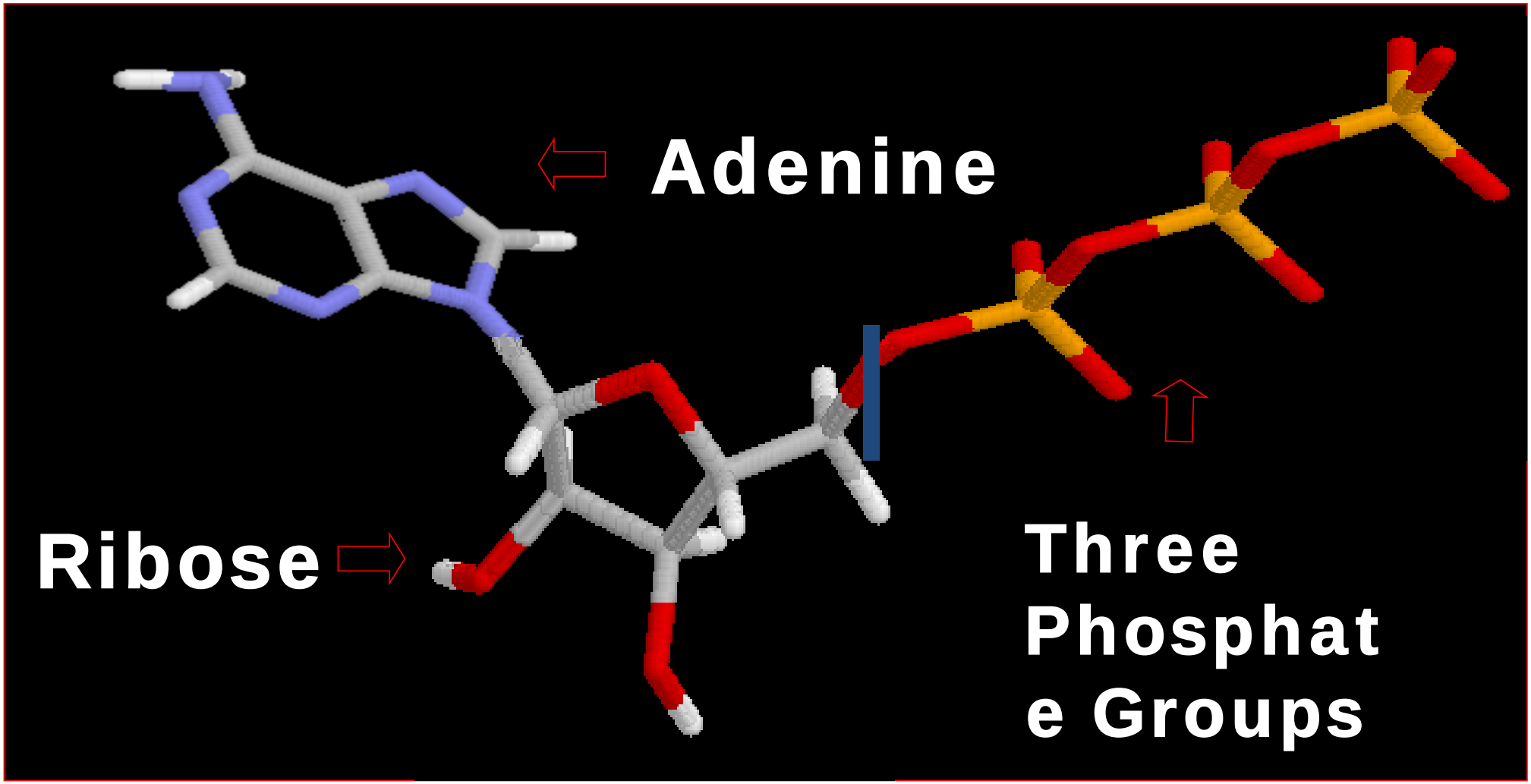
Heart Disease

- 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

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

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 intra-myocardial 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

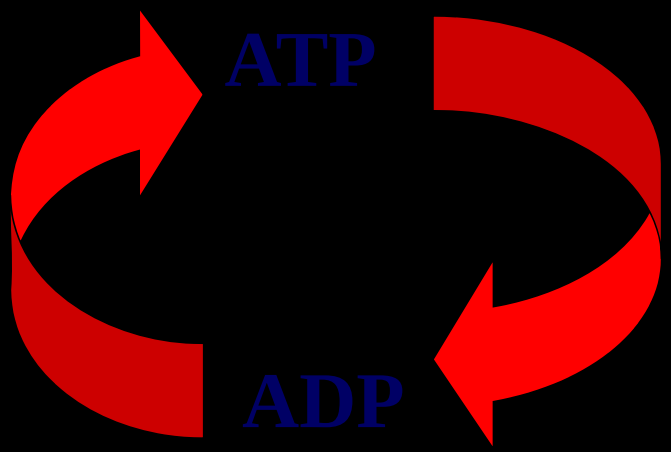
- **D-Ribose**

  The rate-limiting compound in synthesis of new ATP

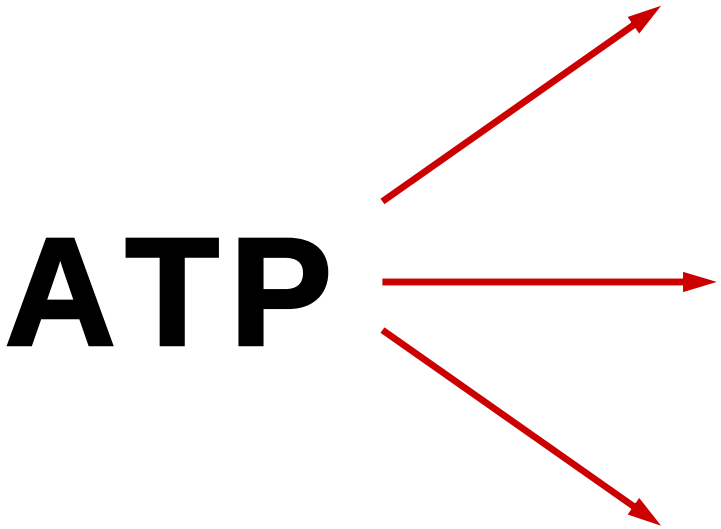
  - *de novo* pathway
  - Salvage pathways

ATP Turnover

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



Role of ATP in Heart Function



Myocardial Function

- **Systolic contraction**
- **Diastolic relaxation**

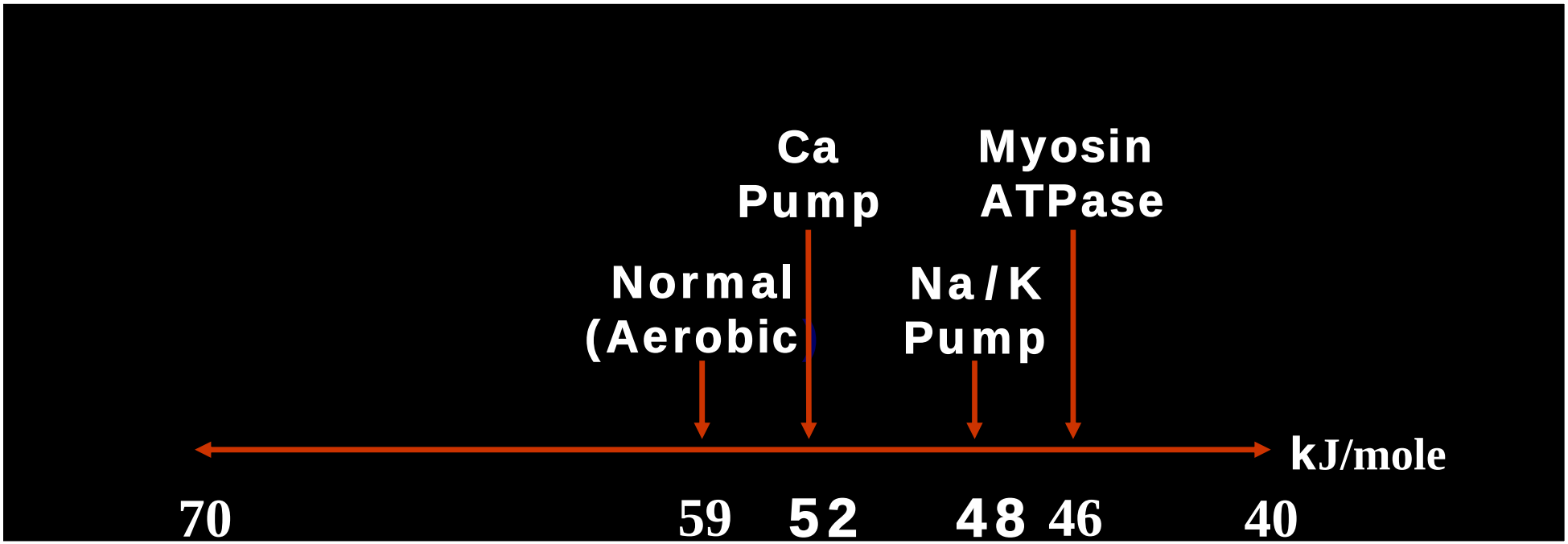
Ion pumps

- **Electrochemical gradients**
- **Ca^{+2} pump**

Biosynthesis

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

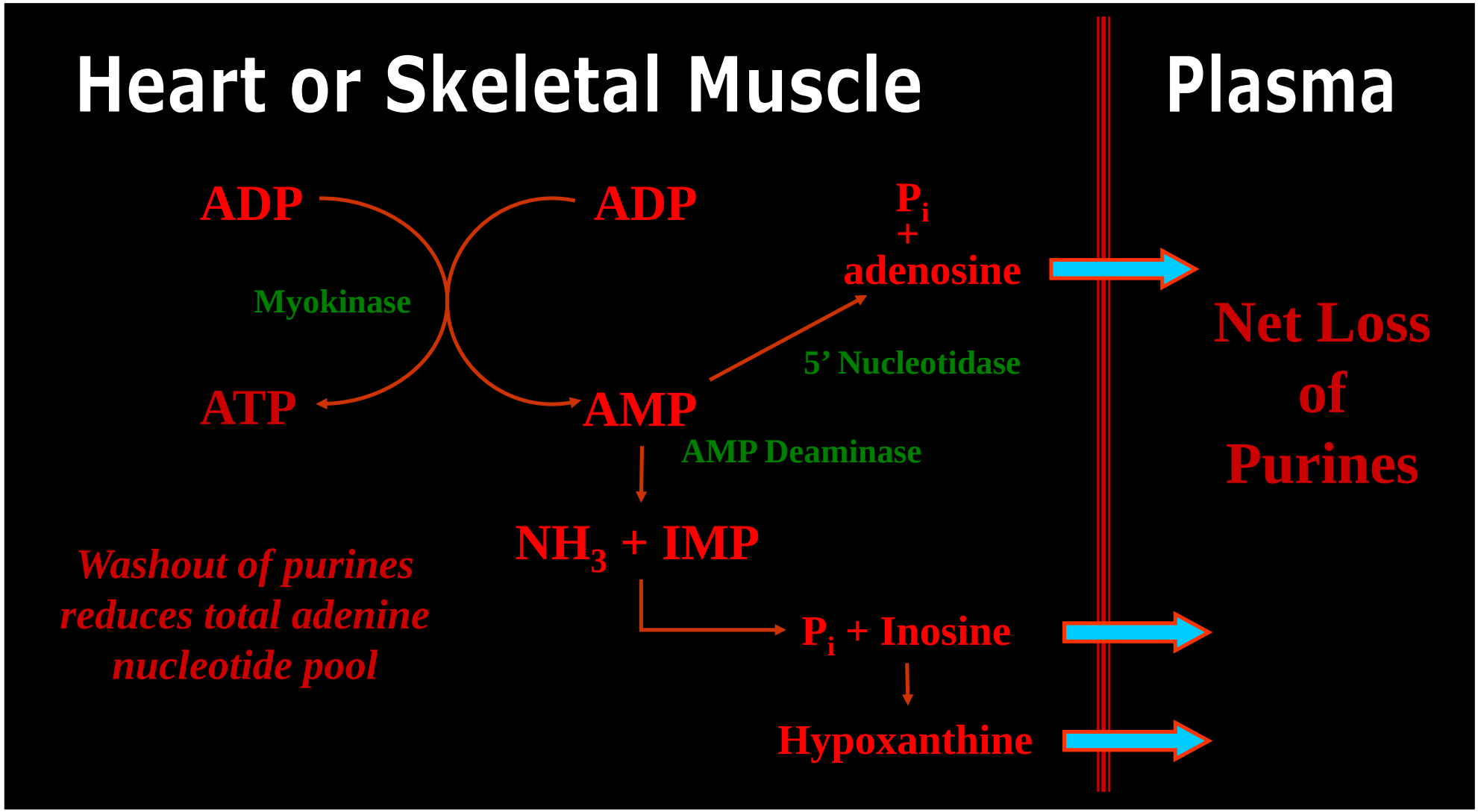
A High [ATP] is the Driving Force Underlying all Cellular Functions



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

Numbers in absolute values

Ischemic Stress Depletes ATP and the Total Adenine Pool



The Solution

Restore the depleted energy substrates to the myocyte with nutriceutical 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

- 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

- 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

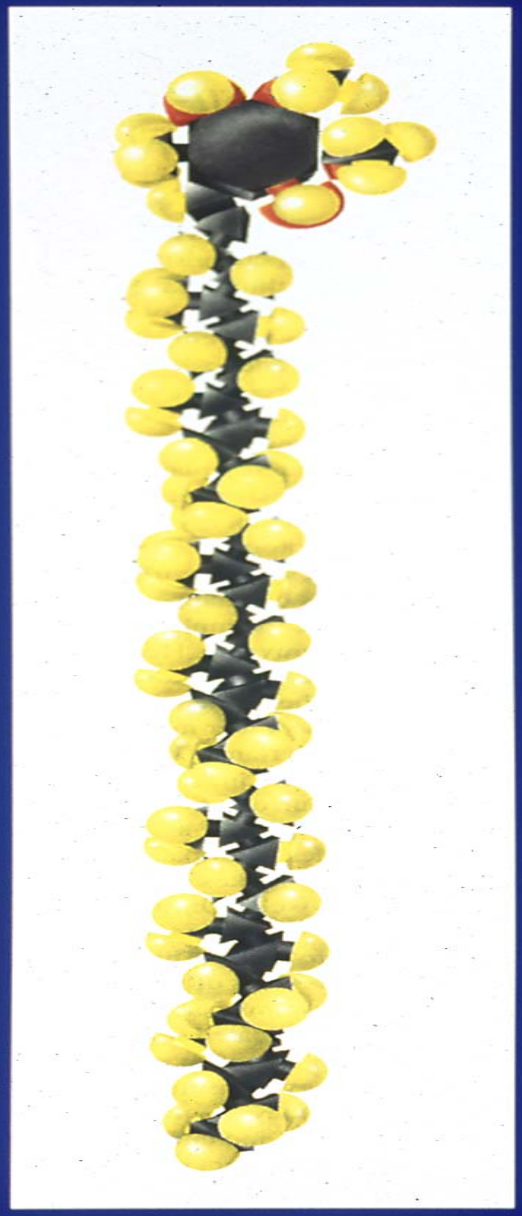
DD Physiological Mechanisms

- 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-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
- 2011 – Q10 reduces oxidative damage in Down’s Syndrome
- 2013 – CoQ10 Rx for CHF Q-SYMBIO Study
- 2014 – 2019 – Explosion of Coenzyme Q10 in medical literature

CoEnzyme Q10 – CV Effects

- Reduces Lp(a)
- Improves endothelial function
- Decreases cholesterol/triglyceride levels
- Increases HDL
- Decreases FBS/HbA1c
- Reduces lipoprotein (LDL) oxidation
- Reduces systolic/diastolic BP

Q-SYMBIO STUDY
Lisbon, Portugal 2014

- 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. JACC (Heart Failure) 2014 Dec;2(6):641-9

My Personal History with CoEnzyme Q10

- Became board-certified cardiologist when Peter Mitchell won the Nobel Prize for Coenzyme Q10 & energy transfer, 1977
- First started using Q10 around 1980 in my patients
- Communicated with Dr. Frederick Crane, Karl Folkers, and Emile Bliznakov in late 80s & 90s
- Lectured around the country on Coenzyme Q10 from early 80s through present. Presented Affinity Award to Karl Folkers mid-90s – A4M
- Published research on bioavailablity-1998

Personal History - continued

- Published anti-aging aspects of Coenzyme Q10 in rat model – 2002
- Published and studied CoQ10 in equine model in 2010-2015
- Utilized Coenzyme Q10 in multiple pediatric patients awaiting transplantation
- Used clinically in thousands of patients over the last 40 years
- CoQ10 is studied extensively and reported in medical literature over its short history of approximately 50 years

Ubiquinone/Ubiquinol/Mito-Q

- Over the years, CoQ10 prototypes such as capsules, captabs, liquids, softgels, chewables
- Emergence of ubiquinol (2006) and Mito-Q approximately ten years ago
- Most important aspect of CoQ10 is BIOAVAILABILITY
- Bioavailability is the essence of CoQ10's remarkable effects
- Studied blood levels in two separate trials - ubiquinone
- Two most quoted studies Q-SYMBIO and Ki-Sel used ubiquinone
- High quality ubiquinone with superb bioavailability is the CoQ10 of choice
- Ubiquinol and Mito-Q perhaps may have advantage in pediatric patients – inborn errors of metabolism

Controlled Trials on Coenzyme Q10 1972-2019

56- Some benefit
4 - No benefit

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

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

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.”

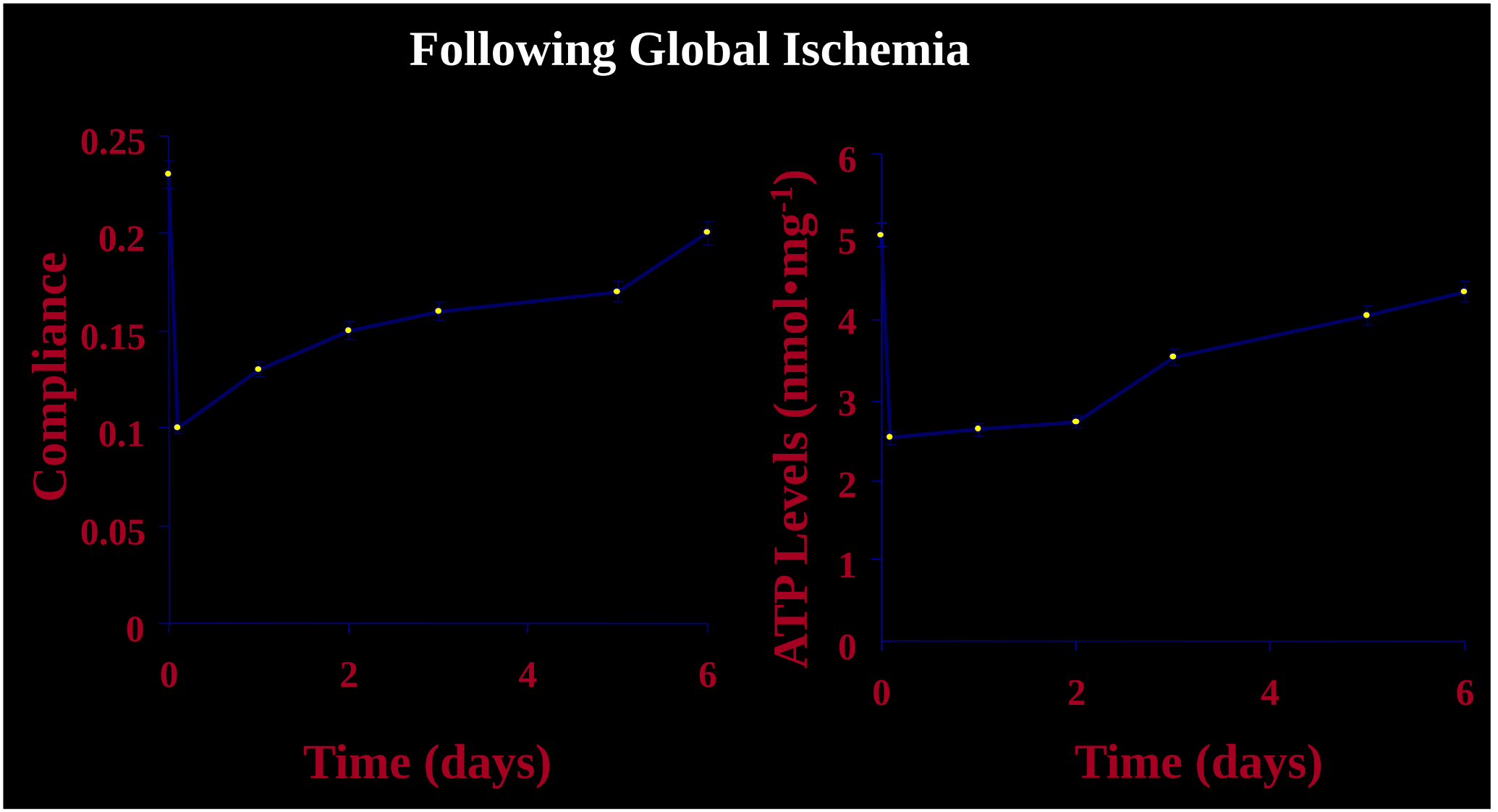
D-ribose

- 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

LV Compliance

Myocardial ATP Levels



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

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

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

Congenital Singlet Outlet Ventricle

- 9 years old Ryan in office – parents distraught
- Moderate to severe CHF
- No heart transplant available x 3
- Metabolic cardiology with Coenzyme Q10, L-carnitine, Magnesium
- D-ribose added in 2005
- Refused HT 3x – now 32 years old

Post-partum Cardiomyopathy

- Case study – Joan 34 year old female status post delivery
- Severe SOB, orthopnea, PND, pedal edema
- Bed to chair capacity – severe CHF
- Typed and crossed for cardiac transplant – MCV
- Started CoQ10 per day – mild improvement
- Doubled & tripled CoQ10 with marked improvement
- Cancelled HT after 6 months of Rx
- EF – 15% → 42% - Still on metabolic card program – 70+ years of age

Diastolic Dysfunction

- Mulit-vitamin/mineral foundation program
- Coenzyme Q10: 100-200 mg
- L-carnitine: 250-500 mg
- D-ribose: 5 grams prior to any strenuous activity
- Magnesium: 400-800 mg
- Calamarine or Fish oil: 2 grams

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