HEARTMD Institute™

From the Desk of Dr. Stephen Sinatra

Metabolic Cardiology: The Missing Link in Cardiovascular Disease *Part 1*

Stephen T. Sinatra, M.D., F.A.C.C., F.A.C.N., C.N.S., C.B.T

Reprinted from Alternative Therapies
March/April 2009, Vol. 15, No. 2

257 East Center Street
Manchester, CT 06040

Phone: 800-228-1507
Fax: 860-643-2531

Email: info@heartmdinstitute.com
www.heartmdinstitute.com

ORIGINAL RESEARCH

METABOLIC CARDIOLOGY: THE MISSING LINK IN CARDIOVASCULAR DISEASE

Stephen T. Sinatra, MD, FACC, FACN

The importance of supporting energy production in heart cells and the preservation of the mitochondria in these cells will be the focus of a new frontier in cardiovascular prevention, treatment, and management. Many physicians are not trained to look at heart disease in terms of cellular biochemistry; therefore, the challenge in any metabolic cardiology discussion is in taking the conversation from the "bench to the bedside." An understanding of the vital role that adenosine triphosphate (ATP) plays in the heart is critical for any physician or clinician considering therapeutic options that support ATP production and turnover in jeopardized cardiac muscle cells.

Metabolic therapies that help cardiomyocytes meet their absolute need for ATP fulfill a major clinical challenge of preserving pulsatile cardiac function while maintaining cell and tissue viability. D-ribose, L-carnitine, and coenzyme Q_{10} work in synergy to help the ischemic or hypoxic heart preserve its energy charge. This article introduces how ATP, diastolic heart function, and metabolic support help maintain cardiac energy by preserving ATP substrates. Part 2 will investigate an in-depth biochemical discussion of congestive heart failure with physiologic, pathophysiologic, and treatment considerations. (*Altern Ther Health Med*. 2009;15(2):48-50.)

Stephen T. Sinatra, MD, FACC, FACN, is an assistant clinical professor at the University of Connecticut School of Medicine in Farmington.

Editor's note: The following is part 1 of a 2-part article. Part 2 will appear in the May/Jun issue of Alternative Therapies in Health and Medicine.

Bioenergetics is the study of energy transformation in living organisms used in the field of biochemistry to reference cellular energy. Understanding the distinction between the concentration of adenosine triphosphate (ATP) in the cell and the efficiency of ATP turnover and recycling is central to our appreciation of cellular bioenergetics. In ischemic or hypoxic hearts, the cell's ability to match ATP supply and demand is disrupted, leading to both depletion of the cardiac energy pool and dysfunction in mitochondrial ATP turnover mechanisms. When ATP levels drop, diastolic heart function deteriorates. Diastolic dysfunction is an early sign of myocardial failure despite the presence of normal systolic function and preserved ejection fraction. High concentrations of ATP are required to activate calcium pumps necessary to facilitate cardiac relaxation and diastolic filling. This observation leads to the conclusion that, in absolute terms, more ATP is needed to fill the heart than to empty it. The absolute requirement for ATP in the context of cardiac conditions in which energy is depleted makes metabolic therapeutic approaches a reasonable intervention.

The metabolic factors associated with myocardial ischemia or hypoxia are profound and have a direct impact on disease pathology. Paramount in this myriad of metabolic challenges is the effect of acute or chronic hypoxia on the cellular bioenergetic pathways that control synthesis, salvage, and recycling of the adenine nucleotides, ATP, adenosine diphosphate (ADP), and adenosine monophosphate (AMP). In ischemic disease, mitochondrial dysfunction and disruption of cardiac energy metabolism deplete cellular energy reserves, with adenine nucleotide levels declining more that 30% in congestive heart failure[1] and 40% or more in coronary artery disease.[2] Tissue biopsy and nuclear magnetic resonance (NMR) findings confirm these observations.[3]

The acute or chronic loss of energy substrates, mitochondrial dysfunction, and disruption of normal energy utilization and supply create conditions of irreversible changes in the cell's biochemical state. Four theories have been advanced that relate to the biochemical changes contributing to the pathology of cardiac disease: (1) a critical energy loss; (2) a critical accumulation of cellular calcium; (3) the effects of free radical formation; and (4) injurious effects of the accumulation of long-chain acyl compounds.[4]

Clearly, a metabolic approach that drives enzymatic reactions in a preferential direction helps to support and restore the vulnerable heart. Such biochemical/metabolic interventions that improve energy metabolism in heart cells will offer the clinician new and exciting treatment options for patients at risk for cardiovascular disease, as well as for patients in any stage of the disease. Once an appreciation of how ATP repairs and restores heart cells is realized, targeted biochemical interventions to support ATP production and turnover will be embellished by physicians. A very brief review of the therapeutic options to promote energy

metabolism and help normalize myocardial adenine nucleotide concentrations will include D-ribose, coenzyme Q_{10}, and L-carnitine. Sicker patients (ie, those with moderate to severe congestive heart failure or ischemia) often will require larger doses of coenzyme Q_{10}, in ranges of 300 mg/d or more, and L-carnintine of 1.5 to 3 g/d in divided doses. In patients with moderate to advanced heart disease, at least 5 g of D-ribose must be given 3 times a day. A more comprehensive review of these therapeutic options will be discussed in part 2 of this article.

D-RIBOSE SUPPORTS CELLULAR ENERGY CHARGE AND PROMOTES DIASTOLIC CARDIAC FUNCTION

Oxygen deprivation leads to the rapid loss of myocardial energy substrates and cellular energy charge.[2] Adenine nucleotide depletion correlates to loss of chemical driving force for biochemical reactions in the cardiomyocyte, initially manifested by dysfunctional calcium management and depressed cardiac diastolic function (Figure 1). The heart's ability to resynthesize ATP and restore the depleted energy pool is limited by the availability of the aldopentose, D-ribose, the carbohydrate structural backbone of adenine nucleotides.

D-ribose is formed in tissue via the oxidative and nonoxidative pentose phosphate pathway of glucose metabolism. D-ribose-5-phosphate, once formed, is converted to 5-phosphoribosyl-1-pyrophosphate (PRPP), stimulating synthesis of purine and pyrimidine nucleotides required by all cells. PRPP is the foundation upon which purine and pyrimidine nucleotides are built.[5,6]

The pentose phosphate pathway is active in tissues that synthesize fatty acids and sterols, such as liver and adrenal cortex. In terminally differentiated myocytes, however, poor expression of the rate-limiting enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase restricts D-ribose synthesis and retards adenine nucleotide recovery in stressed myocardia.[7-9]

D-ribose administration bypasses the rate-limiting steps of the pentose phosphate pathway, increasing the cellular concentration of PRPP required for adenine nucleotide synthesis and salvage. In this way, D-ribose accelerates myocardial adenine nucleotide synthesis, thereby increasing contractile reserve to aid recovery of cardiac diastolic performance (Figures 2 and 3). Clinical studies in patients with ischemic and hypoxic heart disease show that D-ribose administration improves diastolic cardiac function, ventilatory efficiency, myocardial performance index, physical performance, exercise tolerance, and patient quality of life.[10-13]

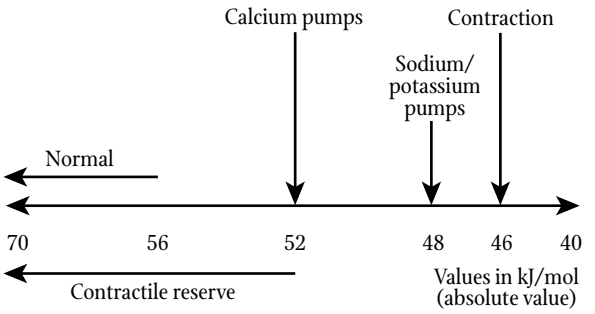

FIGURE 1 The free energy of hydrolysis of ATP (ΔG_{ATP}) required to fuel Ca^{++} ATPase function is high. This explains why high levels of energy are needed to support diastolic cardiac function.

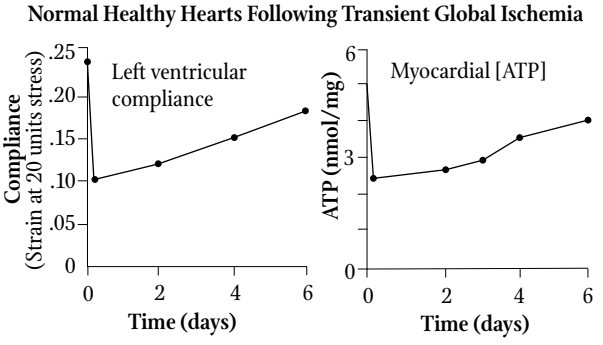

FIGURE 2 A temporal relationship exists between cellular [ATP] and diastolic cardiac function.[14]

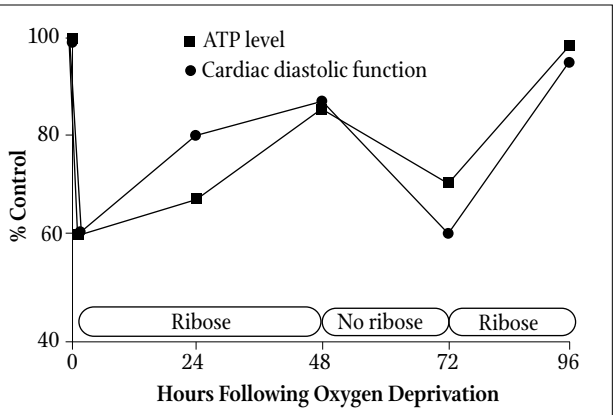

FIGURE 3 D-Ribose administration restores cellular energy charge and diastolic cardiac function.[15]

COENZYME Q_{10} STIMULATES OXIDATIVE METABOLISM AND LIMITS FREE RADICAL DAMAGE

When cardiomyocytes become oxygen deprived, the respiratory turnover of ATP slows. Heart cells respond with pronounced acceleration of glycolytic flux and a shift in energy fuel preference from fatty acids to carbohydrates. This shift in energy production is largely insufficient to compensate for the loss of oxidative ATP turnover in the mitochondria. However, while tissue oxygen tension may be reduced 1000-fold in ischemic hearts, net ATP synthesis can proceed if the mitochondrial proton electrochemical gradient can be maintained in the direction of ATP synthesis over ATP hydrolysis.

Coenzyme Q_{10} is a fundamental, mobile constituent of the electron transport chain of oxidative metabolism that collects reducing equivalents from fixed flavoprotein complexes and passes them on to the cytochromes. The availability of coenzyme Q_{10} is critical for helping to maintain the proton gradient that drives

F_1,F_0-proton ATPase in the direction of ATP synthesis. As such, coenzyme Q_{10} is essential for preserving oxidative ATP synthetic reactions in the ischemic or hypoxic myocardium.

In cardiovascular disease, coenzyme Q_{10} administration helps preserve mitochondrial energy turnover. The result is reduction in free radical formation and peroxide damage[16,17]; increased quality of life in end-stage disease[18]; improved diastolic cardiac function[19]; reduced heart disease hospitalization rates[20]; and lowered incidence of cardiac events, including cardiac death and nonfatal infarction.[21]

L-CARNITINE PROTECTS MITOCHONDRIAL FUNCTION AND ADENINE NUCLEOTIDE TRANSLOCATOR ACTIVITY

Long-chain acyl-CoA esters can enter the mitochondria only in the form of their carnitine esters. The availability of free carnitine is critical for maintaining the intracellular concentrations of long-chain acyl-CoA and long-chain acylcarnitine, thus controlling such basic cellular functions as beta-oxidation of fatty acids in energy metabolism and energy transport from the mitochondria into the cytoplasm via the adenine nucleotide transporter. L-carnitine is also crucial for the removal of toxic metabolites from the mitochondria, helping to preserve mitochondrial membrane integrity and biochemical balance.

Patients with ischemic cardiovascular disease frequently present with myocardial free carnitine deficiency. L-carnitine supplementation increases plasma and myocardial free carnitine levels. In turn, this helps reduce mortality and limit infarct size in patients following myocardial infarction, improves ejection fraction, reduces the incidence of congestive heart failure development, limits arrhythmic events, increases exercise tolerance and reduces incidence of ischemia, and controls free radical formation.[22-26]

CONCLUSION

The energy-starved heart is poorly understood by physicians who treat cardiac disease on a day-to-day basis. Metabolic support with D-ribose, L-carnitine, and coenzyme Q_{10} is critical for the maintenance of contractile reserve and energy charge in minimally oxidative ischemic or hypoxic hearts. Preservation of cellular energy charge provides the chemical driving force required to complete ATPase reactions needed to maintain cell and tissue viability and function. D-ribose, coenzyme Q_{10}, and L-carnitine exert a physiological benefit that has a positive impact on cardiac function. The use of such nutraceutical support for the heart will be of particular importance for physicians who treat cardiovascular disease in their practices. A new, emerging field in metabolic cardiology will be realized as clinicians choose to treat the energy-starved heart at the level of basic energy metabolism.[27] An understanding of these biochemical applications provides the solution for the metabolic treatment of congestive heart failure, which will be reported in part 2 of this article.

Acknowledgment

Thanks to Clarence Johnson for his insightful biochemical contributions to and comments on this paper.

REFERENCES

1. Ingwall JS, Weiss RG. Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circ Res.* 2004;95(2):135-145.
2. Ingwall JS. *ATP and the Heart*. Boston, MA: Kluwer Academic Publishers; 2002.
3. 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(4):734-742.
4. Piper HM, Noll T, Siegmund B. Mitochondrial injury in the ischemic-reoxygenated cardiomyocyte: the role of lipids and other pathogenic factors. In: de Jong JW, R Ferrari, eds. *The Carnitine System: A New Therapeutical Approach to Cardiovascular Diseases*. Boston, MA: Kluwer Academic Publishers; 1995: 101-121.
5. Pauly DF, Pepine CJ. D-Ribose as a supplement for cardiac energy metabolism. *J Cardiovasc Pharmacol Ther.* 2000;5(4):249-258.
6. Pauly DF, Johnson C, St Cyr JA. The benefits of ribose in cardiovascular disease. *Med Hypotheses.* 2003;60(2):149-151.
7. Kalsi KK, Smolenski RT, Yacoub MH. Effects of nucleoside transport inhibitors and adenine/ribose supply on ATP concentration and adenosine production in cardiac myocytes. *Moll Cell Biochem.* 1998;180(1-2):193-199.
8. Zimmer HG. Regulation of and intervention into the oxidative pentose phosphate pathway and adenine nucleotide metabolism in the heart. *Mol Cell Biochem.* 1996 Jul-Aug;160-161:101-109.
9. Zimmer HG. Significance of the 5-phosphoribosyl-1-pyrophosphate pool for cardiac purine and pyrimidine nucleotide synthesis: studies with ribose, adenine, inosine, and orotic acid in rats. *Cardiovasc Drug Ther.* 1998;12 Suppl 2:179-187.
10. Omran H, MacCarter DM, St Cyr J, Lüderitz B. D-Ribose aids congestive heart failure patients. *Exp Clin Cardiol.* 2004;9(2):117-118.
11. Omran H, Illien S, MacCarter D, St Cyr J, Lüderitz B. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. *Eur J Heart Failure.* 2003;5(5):615-619.
12. Carter O, MacCarter D, Mannebach S, et al. D-Ribose improves peak exercise capacity and ventilatory efficiency in heart failure patients. *JACC.* 2005;45(3 Suppl A):185A.
13. Pliml W, von Arnim T, Stäblein A, Hofmann H, Zimmer HG, Erdmann E. Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. *Lancet.* 1992;340(8818):507-510.
14. Mahoney JR Jr. Recovery of postischemic myocardial ATP levels and hexosemonophosphate shunt activity. *Med Hypotheses.* 1990;31(1):21-23.
15. Tveter K, St Cyr J, Schneider J, Bianco R, Foker J. Enhanced recovery of diastolic function after global myocardial ischemia in the intact animal. *J Am Coll Cardiol,* 1989;13(2):130A.
16. Kidd PM, et al. Coenzyme Q_{10}: Essential energy carrier and antioxidant. *HK Biomed Consult.* 1998;1-8.
17. Frei B, Kim MC, Ames BN. Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. *Proc Natl Acad Sci U S A.* 1990;87(12):4879-4883.
18. Berman M, Erman A, Ben-Gal T, et al. Coenzyme Q_{10} in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study. *Clin Cardiol.* 2004;27(5):295-299.
19. Langsjoen H, Langsjoen P, Langsjoen P, Willis R, Folkers K. Usefulness of coenzyme Q_{10} in clinical cardiology: a long-term study. *Mol Aspects Med.* 1994;15 Suppl:S165-S175.
20. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: A long-term multicenter randomized study. *Clin Investig.* 1993;71(8 Suppl):S134-S136.
21. Singh RB, Neki NS, Kartikey K, et al. Effect of coenzyme Q_{10} on risk of atherosclerosis in patients with myocardial infarction. *Mol Cell Biochem* 2003;246(1-2):75-82.
22. Davini P, Bigalli A, Lamanna F, Boem A. Controlled study on L-carnitine therapeutic efficacy in post-infarction. *Drugs Exp Clin Res.* 1992;18(8):355-365.
23. Singh RB, Niaz MA, Agarwal P, Beegum R, Rastogi SS, Sachan DS. A randomised, double-blind, placebo-controlled trial of L-carnitine in suspected myocardial infarction. *Postgrad Med J.* 1996;72(843):45-50.
24. Cacciatore L, Cerio R, Ciarimboli M, et al. The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: a controlled study. *Drugs Exp Elin Res.* 1991;17(4):225-235.
25. Seidman MD, Khan MJ, Bai U, Shirwany N, Quirk WS. Biologic activity of mitochondrial metabolites of aging and age-related hearing loss. *Am J Otol.* 2000;21(2):161-167.
26. Iliceto S, Scrutinio D, Bruzzi P, et al. Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-carnitine Ecocardiografia Digitalizzata Infarto Miocardioco (CEDIM) trial. *J Am Coll Cardiol.* 1995;26(2):380-387.
27. Sinatra S. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study. *Clin Cardiol.* 2004;27(10):A26; author reply A26, A30.