Metabolic Cardiology:
The Missing Link in Cardiovascular Disease

Part 1

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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 Q10 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.

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metabolism and help normalize myocardial adenine nucleotide concentrations will include D-ribose, coenzyme Q₁₀, and L-carnitine. Sicker patients (i.e., those with moderate to severe congestive heart failure or ischemia) often will require larger doses of coenzyme Q₁₀ in ranges of 300 mg/d or more, and L-carnitine 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. 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.

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.

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.

COENZYME Q₁₀ 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 Q₁₀ 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 Q₁₀ 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; increased quality of life in end-stage disease; improved diastolic cardiac function; reduced heart disease hospitalization rates; and lowered incidence of cardiac events, including cardiac death and nonfatal infarction.

L-CARNITINE PROTECTS MITOCHONDRIAL FUNCTION AND ADENINE NUCLEOTIDE TRANSLATOR 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.

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. 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.

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REFERENCES

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