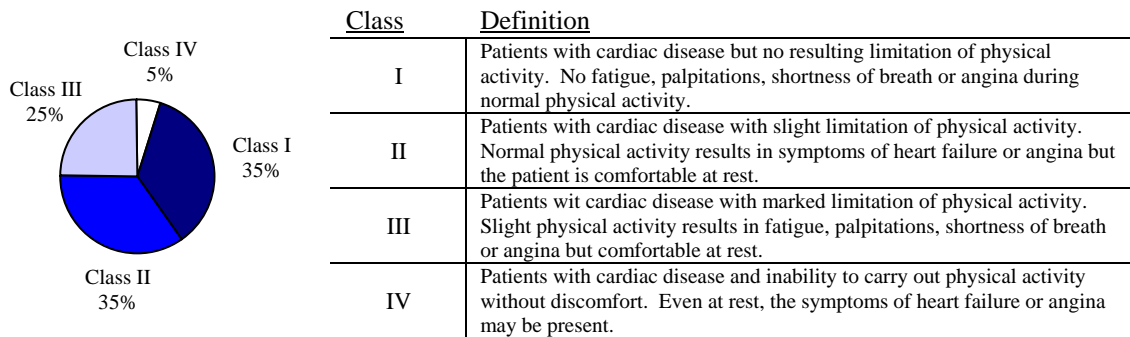


D-Ribose in Congestive Heart Failure and Ischemic Disease

Congestive heart failure (CHF) is a disease caused by weakening of the heart muscle making it unable to pump a sufficient volume of blood to supply the body's need for oxygen. Cardiovascular diseases such as hypertension, coronary artery disease and cardiomyopathy often lead to the onset of CHF causing both systolic and diastolic cardiac dysfunction. Nearly all patients with systolic dysfunction also present with some degree of diastolic dysfunction, specifically impaired relaxation and loss of ventricular compliance.

The severity of CHF is defined by New York Heart Association (NYHA) classification falling into four categories as shown in Figure 1. A recent study conducted at the Mayo Clinic, Rochester, Minnesota reported that 25% of all adults over age 45 in the U.S. exhibit mild to severe symptoms of diastolic dysfunction and CHF. However, less than half of those presenting with even moderate or severe diastolic or systolic dysfunction had recognized CHF or knew they were at risk. The authors conclude that 20% of people over age 40 are at risk for developing CHF during their lifetime and that the presence or absence of diastolic dysfunction, regardless how severe, is predictive of all-cause mortality.

Figure 1: NYHA Classification of Congestive Heart Failure Severity



The Mayo study went on to conclude that patients showing even mild preclinical diastolic cardiac dysfunction have an 8-fold higher chance of death within five years than normal, healthy adults and those with moderate or severe symptoms have a 10 fold greater probability of death.

Drug Treatments Only Slow the Progression of the Disease

Clinical studies show that drug treatment can lower the extremely high mortality of CHF, but no treatment options exist that will cure the disease. Heart transplants are used in a small number of patients, but in the U.S. only 2,200 heart transplants are performed annually with tens of thousands of patients on the waiting list. Additionally, drug therapy is limited in its ability to keep up with progression of disease symptoms and physicians are frequently faced with quickly maximizing dosages while losing the battle with progression. Once maximum dose levels are reached, physicians have few treatment options.

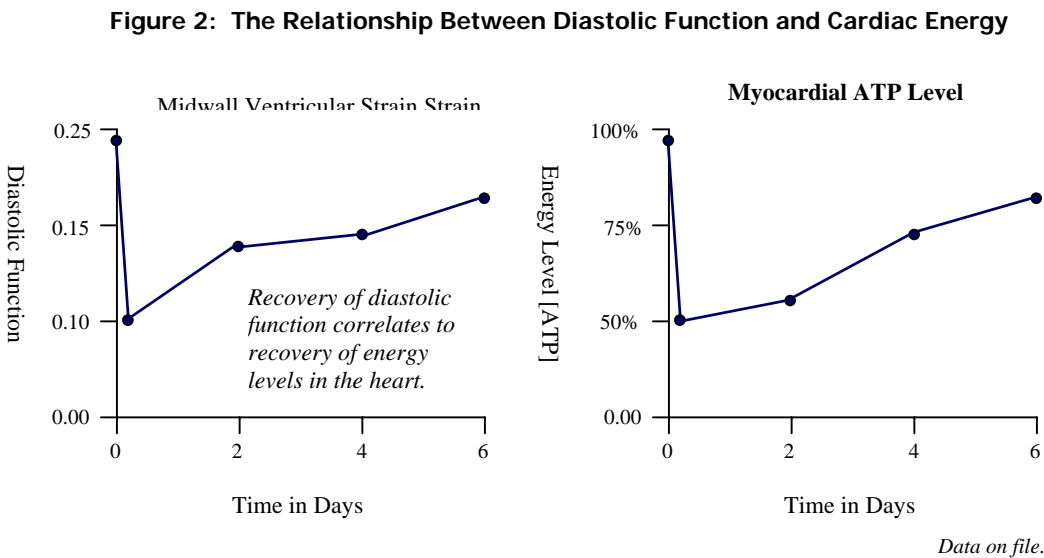
Electrophysiological options are now available to synchronize heartbeats to slow disease progression. Biventricular cardiac pacing is a new medical device option that places electrodes in both ventricles of

the heart to synchronize the heartbeat and relieve symptoms of CHF. These devices are shown to improve exercise tolerance and quality of life in patients with CHF but only limited studies are available, making long term conclusions risky.

Major investment is currently moving into this space. For example, recent technology has been introduced in the US designed to safely remove fluid from patients hospitalized for fluid overload associated with CHF. In addition, external counter pulsation devices are now approved in the US to provide left ventricular assist and relieve cardiac preload pressures in CHF. Until Bioenergy introduced CORvalen™ in mid-2002, however, no metabolic alternatives to drug treatment have made their way to the market.

The Effect of Cardiac Energy on Diastolic Dysfunction

Ischemic heart disease and congestive heart failure lead to a progressive decline in the heart’s ability to maintain normal energy pools. A direct temporal relationship exists between the energy level of the heart and diastolic function as measured by ventricular compliance and ventricular wall thickening. Figure 2 gives evidence of this relationship.



Energy is important in diastole due to its effect in regulating the physiological activity of ion pumps found on the surface of the heart cell. When the heart contracts, calcium from outside the cell floods to the inside providing the necessary mechanism for contraction. To allow relaxation and refilling of the ventricle this calcium must be removed. Because the concentration of calcium outside the cell is much greater than inside, removing calcium against the concentration gradient requires active pumping. These calcium pumps are fueled by energy. Other similar physiological mechanisms having to do with ion balance and maintaining cell wall integrity are also disrupted or lost when energy levels are reduced due to hypoxia or ischemia.

Table 1 describes how the loss of energy in heart cells affects important physiological parameters. In reviewing the tables, note that the larger the negative number, the greater the energy reserve or energy required to perform the function. For example, an energy requirement to fuel calcium pumps (-52 kJ/mol) is high, while that needed for contraction (-46 kJ/mol) is low. Further note that the energy level in healthy control hearts (-58 kJ/mol) does not provide a great deal of reserve capacity

relative to maintaining normal function of ion pumps. A significant contractile reserve exists, however, meaning that hearts will beat with depressed energy stores but will not function normally.

Energy within the heart cell is not homogenous. Instead it exists in discrete pools. Simply put, while a certain amount of energy sharing exists between the pools in general one pool is associated with contraction while a separate pool maintains cell wall function, such as fueling ion pumps. Energy for contraction is preferential to that associated with cell wall function, so it is the cell wall mechanisms that are first disrupted when energy levels in the cell become depleted.

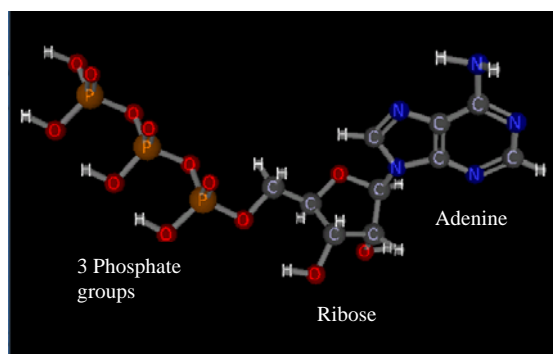
Tables 1: The Need for Energy to Fuel Basic Physiological Functions in the Heart²

Energy Needed to Fuel Physiological Function in the Heart under Controlled Conditions		Relative Need for Maximal Energy in the Cell	Effect of Ischemia and Hypoxia on Heart Energy Levels	
Calcium pumps	-52 kJ/mol	High	Control	-58.4 kJ/mol
Sodium/Potassium pumps	-48 kJ/mol	Medium	12 minutes hypoxia (pO ₂ ~20 Torr)	-51.6 kJ/mol
Contraction	-46 kJ/mol	Low	12 minutes zero-flow ischemia	-43.7 kJ/mol

The Role of Ribose in Maintaining Cardiac Energy

The role of ribose in regulating energy synthesis gives it a special significance unlike any other carbohydrate. Ribose is not a fuel used to recycle energy nor is it a simple participant in the energy pathways. Instead, ribose is a substrate that regulates and controls the synthesis of energy compounds.

Figure 3: The Energy Compound Adenosine Triphosphate (ATP)



ATP is the primary energy compound used by the body to fuel normal physiological function.

Ribose is an integral component of the ATP molecule and regulates its synthesis.

Most tissues in the body, including the heart, are unable to produce ribose fast enough to quickly restore energy levels once they are depleted. If ribose is not readily available to the tissue the synthetic processes for restoring lost energy are depressed. Ribose is made naturally in the body from the simple sugar, glucose. The metabolic pathway used to make ribose naturally is slow and inefficient because these tissues lack certain enzymes required to drive the pathway. Providing

exogenous ribose to these tissues is proven to enhance their ability to normalize energy pools once they have been reduced or depleted.

A large body of scientific evidence proves that ribose regulate the energy synthetic pathways. The following figures are reflective of these findings. Figure 4 shows that immediately following ischemia energy levels in the heart are depressed and diastolic function is significantly reduced. Providing ribose to these hearts (in a live, closed chest canine heart model) allows the heart to regain both its energy level and diastolic function. If ribose is removed, energy and function again become depressed. However, re-supply of ribose allows the heart to quickly recover.

Figure 4: The Effect of Ribose on Energy and Diastolic Function in Working Hearts

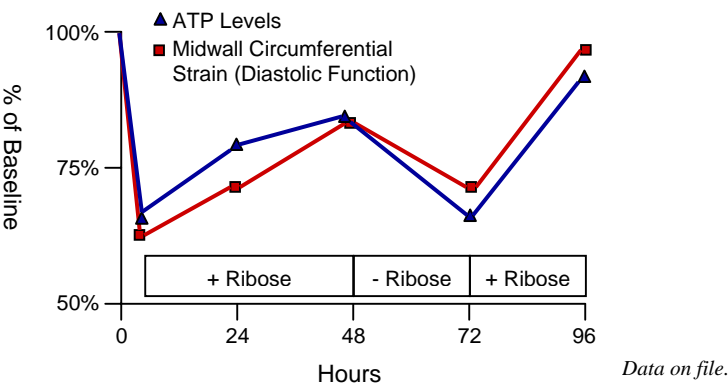
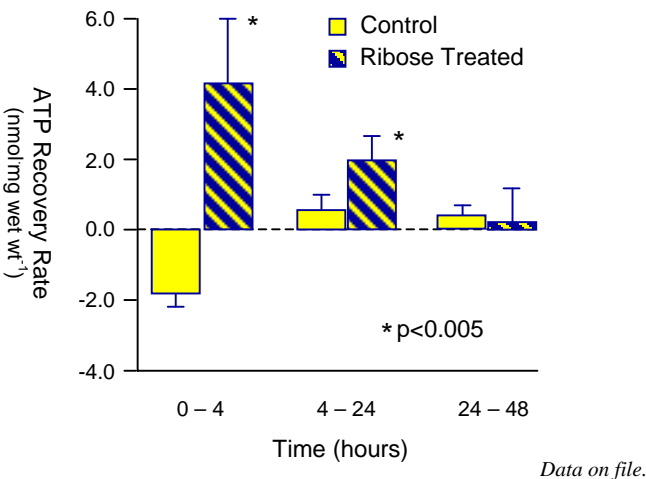


Figure 5 gives direct evidence of the role of ribose in replacing energy pools that are lost to ischemia. It is well known that ischemia or hypoxia severely depress cardiac energy levels. Immediately following ischemia hearts that are given ribose rapidly re-build their energy pool. In this study the energy pool of test hearts was completely restored within 24 hours. Hearts that were not given ribose showed a continuing loss of energy reserves for the first four hours before slowly beginning to re-build. The speed with which these control hearts were able to re-build energy reserves was directly related to their ability to produce ribose naturally. In this study it took an average of 9.8 days for the energy pools to recover in control hearts.

Figure 4: The Effect of Ribose on Cardiac Energy Recovery



Human clinical trials show similar results, although fully exhaustive studies have not yet been conducted. A study published in *Lancet* used patients with coronary artery disease and stable angina to investigate the effect of ribose on exercise tolerance, time to angina and time to electrocardiographic change (S-T segment depression) indicative of cardiac ischemia. When patients were given ribose (at high doses of 60-grams per day) they showed significant improvement in exercise tolerance and were able to exercise longer before onset of angina or S-T segment depression.

Mid-study results of an ongoing double blind, crossover trial with congestive heart failure patients were recently reported. Results showed conclusively that when patients were given ribose (15-grams/day for three weeks) they had improved diastolic heart function, increased physical function score and enhanced quality of life score. Echocardiographic studies of these patients showed that ribose administration enhanced relaxation of the left ventricle and improved the efficiency of filling from the left atrium. No such improvements were found during placebo administration.

The physiological benefit of ribose administration is clear. Ribose supplementation improves diastolic heart function, increases exercise tolerance and enhances patient quality of life. These benefits are provided by the role ribose plays in increasing cardiac energy reserves that become depressed during ischemia or hypoxia associated with coronary artery disease or congestive heart failure.

Opportunity

For congestive heart failure alone, an estimated five million people suffer from the condition in the US, incurring 3.1 million hospital admissions at a cost of over \$23 billion annually. With the aging population, CHF diagnoses in the US are growing at 8% per year. A similar prevalence exists in Europe. Congestive heart failure and ischemic heart disease are of grave concern to both patients and their families, significantly reducing patient quality of life. Diastolic dysfunction is evident in 75% of patients suffering congestive heart failure, it is a major symptom of ischemic cardiomyopathy and is almost universal in patients with coronary artery disease affecting the left ventricle.

In the U.S., 25% of all adults over age 45 show evidence of diastolic dysfunction. In most cases this condition goes unheeded. Comparing a major study conducted in North Glasgow, Scotland with the Mayo Clinic data (taking into account age and sex of participants and study technique) the prevalence in Europe appears to be similar.

Ribose goes directly to preserving healthy energy pools needed to maintain diastolic function. No other compound regulates the energy synthetic pathways necessary to perform this important, and vital, metabolic function. Clinical studies have shown that ribose supplementation has a direct impact on cardiac diastolic function, physical function and quality of life in patients suffering from CHF and ischemic disease and should be included in treatment regimens. Further, understanding that preclinical symptoms of diastolic dysfunction often go unnoticed, every at risk adult should be supplemented with ribose to maintain or stabilize cardiac energy reserves needed to promote healthy diastolic heart function.

The opportunity for using ribose to combat diastolic dysfunction is dramatic and should be seized upon.

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