Metabolic Cardiology:
An Integrative Strategy
in the Treatment of
Congestive Heart Failure
Part 2

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METABOLIC CARDIOLOGY:
AN INTEGRATIVE STRATEGY IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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Congestive heart failure (CHF) and dilated cardiomyopathy are life-threatening conditions in which the heart muscle is so weak that effective pulsatile action is compromised. Pulmonary vascular congestion and swelling in the lower extremities as well as in the liver and lining of the gastrointestinal tract frequently cause overwhelming symptoms and disability. Millions of Americans suffer from CHF, and more than 500 000 cases are diagnosed annually. Cardiovascular diseases such as hypertension with left ventricular hypertrophy, valvular heart disease, coronary artery disease, myocarditis, and various cardiomyopathies can lead to the progressive onset of CHF.

The purpose of this article is to introduce metabolic cardiology as a vital therapeutic strategy using nutritional biochemical interventions that preserve and promote adenosine triphosphate (ATP) production. Treatment options that incorporate metabolic interventions targeted to preserve energy substrates (D-ribose) or accelerate ATP turnover (L-carnitine and coenzyme Q10) are indicated for at-risk populations or patients at any stage of CHF. The integration of these metabolic supports provides the missing link in CHF treatment that has been eluding physicians for decades. (*Altern Ther Health Med*. 2009;15(3):44-52.)

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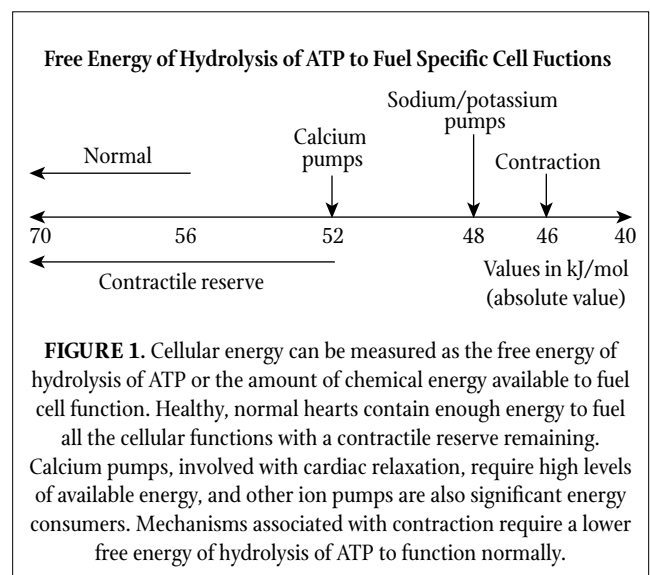
Congestive heart failure (CHF) is accompanied by systolic and/or diastolic dysfunction. Most clinicians usually have no difficulty understanding and diagnosing systolic dysfunction; abnormalities can be easily detected by a careful physical examination and chest x-ray. However, diastolic dysfunction is more insidious and difficult to diagnose. Symptoms of diastolic dysfunction, such as shortness of breath or easy fatigability, may be expressed several years before the diagnosis is actually determined by careful echocardiographic analysis of the mitral valve. Diastolic dysfunction reflects impairment in the filling phase of the cardiac cycle.

As counterintuitive as it may sound, it is important to note that stretching and filling the heart chambers with blood (diastole) requires much more energy—or adenosine triphosphate (ATP)—than does contracting and emptying the heart chambers (systole). Higher concentrations of ATP are required to activate the calcium pump activity necessary to facilitate cardiac relaxation and diastolic filling (Figure 1).

As ATP concentrations decline in cardiomyocytes, gradual

and insidious diastolic dysfunction of the left ventricle often results. Cardiovascular bioenergetic cellular energy levels can be measured as a free energy from the hydrolysis of ATP or as the amount of chemical energy available to sustain cellular function.

Both systolic and diastolic dysfunction are frequently undiagnosed until the clinical onset of overt heart failure.[1] It has recently been reported that 28% of the population, male and female, over the age of 45 years has mild-to-moderate diastolic dysfunction despite a well-preserved ejection fraction. At the

Free Energy of Hydrolysis of ATP to Fuel Specific Cell Fuctions

FIGURE 1. Cellular energy can be measured as the free energy of hydrolysis of ATP or the amount of chemical energy available to fuel cell function. Healthy, normal hearts contain enough energy to fuel all the cellular functions with a contractile reserve remaining. Calcium pumps, involved with cardiac relaxation, require high levels of available energy, and other ion pumps are also significant energy consumers. Mechanisms associated with contraction require a lower free energy of hydrolysis of ATP to function normally.

Integrative Treatment for Congestive Heart Failure

same time, 8% present with ejection fractions of 50% or lower, levels indicating moderate to severe systolic dysfunction. Yet even among those with moderate to severe systolic or diastolic dysfunction, less than 50% of the 2042 subjects involved had been diagnosed with documented CHF. To identify the magnitude of this critical medical problem, researchers projected that the lifetime risk of developing CHF for those over the age of 40 years to be 20%, a level well in excess of many conditions commonly associated with age.[1]

It is now widely accepted that one key characteristic of the failing heart is the persistent and progressive loss of energy. Because the requirement for energy to support the systolic and diastolic work of the heart is absolute, it logically follows that a disruption in cardiac energy metabolism and the energy supply/demand mismatch that results can be identified as the pivotal factor contributing to the inability of failing hearts to meet the hemodynamic requirements of the body.

In her landmark book, *ATP and the Heart*, Joanne Ingwall, PhD, describes the metabolic maelstrom associated with the progression of CHF and identifies the mechanisms that lead to a persistent loss of cardiac energy reserves as the disease process unfolds.[2] It is largely concluded that the overt loss of energy substrates, coupled with modifications in the biochemical methods by which cardiomyocytes manage their energy loads, is closely linked to cardiac function in this disease state.

BASICS OF CARDIAC ENERGY METABOLISM

The heart consumes more energy per gram than any other organ, and the chemical energy that fuels the heart comes primarily from ATP. ATP is composed of 3 chemical moieties: D-ribose, a pentose monosaccharide that provides the structural foundation of the molecule; adenine, a purine base; and 3 phosphoryl groups held loosely together in a series by phosphoryl bonds. The chemical energy generated and released during ATP metabolism is stored in the phosphoryl bonds, with the greatest amount of this ATP energy residing in the outermost bond that holds the ultimate phosphoryl group to
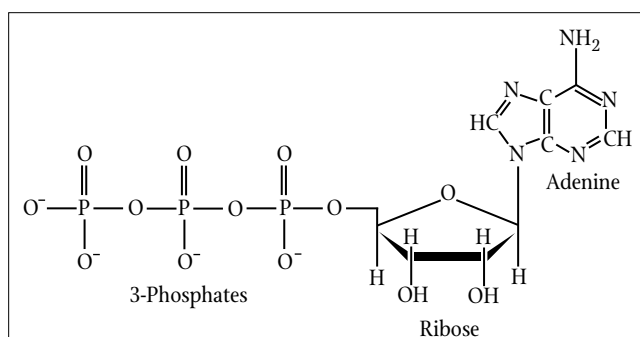

FIGURE 2. The ATP molecule is composed of D-ribose as its carbohydrate structural core, adenine, and 3 phosphoryl groups. Chemical energy is released when the chemical bond attaching the ultimate phosphoryl group to the penultimate group. Chemical energy is converted to mechanical energy for cell work.

the penultimate group (Figure 2).

When energy metabolism is required to provide the chemical driving force to a cell, this ultimate phosphoryl bond is broken, and chemical energy is released. The cell then converts this chemical energy "fuel" to perform the mechanical energy specific to each cell's function. In the case of the heart, the energy is used to conduct an electrical charge, sustain contraction, drive ion pump function, synthesize large and small molecules, and perform other necessary activities of the cell. The consumption of ATP in the generation of cellular energy yields the metabolic by-products adenosine diphosphate (ADP) and inorganic phosphate (Pi). A variety of metabolic mechanisms have evolved within the cell to provide rapid rephosphorylation of ADP in order to restore ATP levels and maintain the cellular energy pool. In significant ways, these metabolic mechanisms are disrupted in CHF, tipping the balance in a manner that creates a chronic energy supply/demand mismatch.

ATP, ADP, and the most basic adenine nucleotide metabolite, adenosine monophosphate (AMP), belong to a class of biochemical compounds known as adenine nucleotides. Combined, they form the total adenine nucleotide (TAN) pool of the cell, and the size and makeup of the pool is what defines the cell's chemical driving force.

The normal heart is capable of maintaining a stable ATP concentration despite large fluctuations in workload and energy demand. In a normal heart, the rate of ATP synthesis via rephosphorylation of ADP closely matches ATP utilization. The primary site of intracellular ATP rephosphorylation is the mitochondria, where fatty acid and carbohydrate metabolic products flux down the oxidative phosphorylation pathways. Additionally, ATP recycling can occur in the cytosol, by way of the glycolytic pathway of glucose metabolism. In normal hearts, this pathway accounts for only about 10% of ATP turnover. Phosphoryl transfer between sites of ATP production and utilization also occurs via other mechanisms, the most predominant of which is the creatine kinase (CK) reaction in which a high-energy phosphate is translocated from creatine phosphate (PCr) to ADP to yield ATP and free creatine. Because the CK reaction is approximately 10-fold faster than ATP synthesis via oxidative phosphorylation, creatine phosphate acts as a buffer to ensure a consistent availability of ATP in times of acute high metabolic demand. The various ATP synthetic pathways function to maintain a high level of ATP availability and to balance the ratio of ATP to its metabolites, ADP and Pi. The ATP:ADP ratio, coupled with the intracellular Pi concentration, is a key variable in terms of maintaining a high chemical driving force for the cellular energy, which is essential for normal myocyte function and viability. Increases in ADP and Pi lower the chemical driving force of the cell and, therefore, tend to activate ATP synthetic pathways. Lower levels of ADP relative to ATP concentration tend to downregulate these pathways.

The tissue content of ATP progressively decreases in CHF, frequently reaching and then stabilizing at levels that are 25% to 30% lower than normal.[3,4] The fact that ATP decreases in the failing heart means that the metabolic network responsible for maintaining the

balance between energy supply and demand is no longer functioning normally. It is well established that oxygen deprivation in ischemic hearts contributes to the depletion of myocardial energy pools,[2,4] but the loss of adenine nucleotides in the failing heart is a unique example of chronic metabolic failure in the well-oxygenated myocardium. The proximal mechanism explaining TAN depletion in heart failure is through activation of the gatekeeper enzyme of the adenine pool, cytosolic AMP-dependent 5'-nucleotidase (5'-NT), which converts AMP to adenosine. In conditions where energy demand outstrips supply, ATP is consumed at a faster rate than it can be restored via oxidative phosphorylation or the alternative pathways of ADP rephosphorylation. The result of this overconsumption is an increase in ADP concentrations that, in turn, activate adenylate kinase, an enzyme catalyzing a reaction that shifts a phosphoryl group from one ADP to a second ADP, yielding ATP and AMP. The ATP formed by this reaction enters the ATP pool, but the AMP becomes substrate for 5'-NT in a reaction yielding adenosine. Adenosine is subsequently converted to inosine and hypoxanthine. Unlike phosphorylated nucleotides that cannot cross the cell membrane, adenosine, inosine, and hypoxanthine cross readily and exit the cell following their concentration gradient. This loss of catabolic by-products lowers the cellular concentration of adenine nucleotides and depletes energy reserves. In diseased hearts, the energy pool depletion via this mechanism can be significant, reaching levels that exceed 40% in ischemic heart disease (Figure 3) and 30% in heart failure (Figure 4).
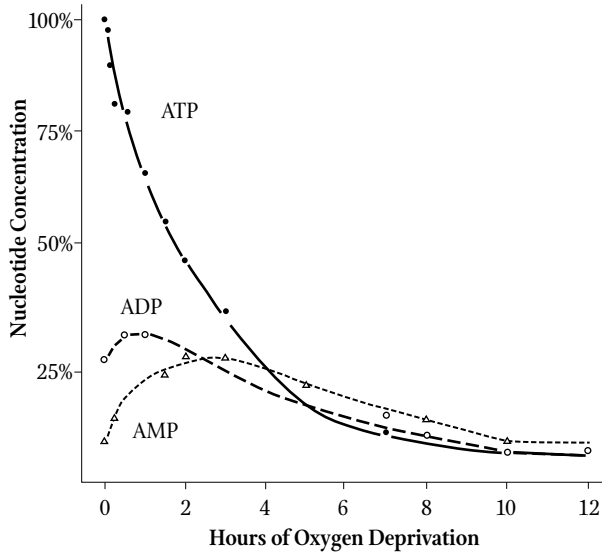
Under high workload conditions, even normal hearts display a minimal loss of purines that must be restored via the *de novo* pathway of purine nucleotide synthesis. This pathway is slow and energetically costly, requiring consumption of 6 high-energy phosphates to yield 1 newly synthesized ATP molecule. The slow speed and high energy cost of *de novo* synthesis highlights the importance of cellular mechanisms designed to preserve adenine nucleotide pools. In normal hearts, the salvage pathways are the predominant means by which the adenine nucleotide pool is maintained. Whereas *de novo* synthesis of ATP proceeds at a rate of approximately 0.02 nM/min/g in the heart, the salvage pathways operate at a 10-fold higher rate.

Salvage pathways are biochemical routes, typically involving only one enzyme, through which preformed purine bases and nucleotides are returned to the adenine nucleotide pool. Through the salvage pathway, adenine, hypoxanthine, and guanine can be captured, rephosphorylated, and returned to the high-energy phosphate pool before they can leave the cell.[5] In this way, the energy pool of the cell is preserved. Salvage of hypoxanthine and guanine is via the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT), and adenine occurs via adenine phosphoribosyltransferase (APRT). The expression of both HGPRT and APRT is limited by the cellular availability of 5-phosphoribosyl-1-pyrophosphate (PRPP). PRPP initiates purine nucleotide synthesis and salvage and is the sole compound capable of donating the D-ribose-5-phosphate moiety required to re-form adenine nucleotides and preserve the energy pool.
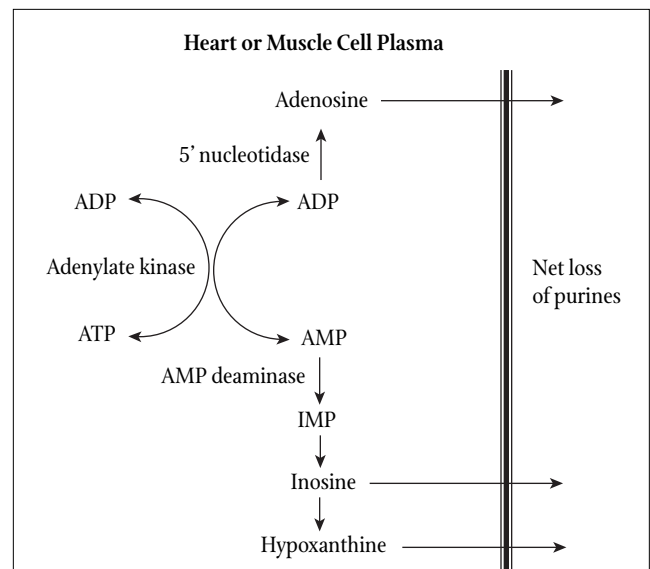

FIGURE 3. During periods of ischemia or hypoxia, cells use energy faster than it can be recycled. This example of severely oxygen-starved hearts shows that as ATP levels fall, the concentration of ADP rises in the cell. As ADP is depleted, AMP levels rise. Finally, AMP is fully used up, and the by-products leave the cell. The total concentration of energy compounds (ATP + ADP + AMP) falls dramatically as the energy substrates are washed out of the cell. Adapted with permission from Ingwall JS. *ATP and the Heart*. Boston, MA: Kluwer Academic Publishers; 2002.

FIGURE 4. When the cellular concentration of ATP falls and ADP levels increase, 2 molecules of ADP can combine. This reaction provides one ATP, giving the cell additional energy, and one AMP. The enzyme adenylate kinase (also called myokinase) catalyzes this reaction. The AMP formed in this reaction is then degraded and the by-products are washed out of the cell. The loss of these purines decreases the cellular energy pool and is a metabolic disaster to the cell.

ENERGY STARVATION IN FAILING HEARTS

Heart failure is typically associated with an overstretched, thickened, and enlarged left ventricle, or left ventricular hypertrophy (LVH), a situation that overtaxes the heart muscle with each contraction. The long-term mechanism explaining the loss of ATP in CHF is decreased capacity for ATP synthesis relative to ATP demand. In part, the disparity between energy supply and demand in hypertrophied and failing hearts is associated with a shift in relative contribution of fatty acid vs glucose oxidation to ATP synthesis. The major consequence of the complex readjustment toward carbohydrate metabolism is that the total capacity for ATP synthesis decreases, while the demand for ATP continually increases in the failing and hypertrophied heart. The net result of this energy supply/demand mismatch is a decrease in the absolute concentration of ATP in the failing heart. This decrease in absolute ATP level is reflected in lower energy reserve in the failing and hypertrophied heart.

In a series of studies investigating bioenergetic abnormalities in left ventricular (LV) remodeling and in periinfarct regions of the myocardium, Gourine et al confirmed their hypothesis for defining the mechanism for energy depletion in the failing and hypertrophied heart. In one study, LV remodeling was induced by ligation of the coronary artery, and cardiac microdialysis was used to assess changes in interstitial purine metabolite concentrations at rest and in response to high workload resulting from intravenous isoproterenol induction.[6] The study revealed that resting concentrations of interstitial purine metabolites were higher in study animals than in sham-operated controls and after isoproterenol stimulation, the concentrations of purine metabolites were further elevated in the study animals. This study showed that the mismatch of energy supply to demand was persistent in remodeled ventricular tissue and was exacerbated during high workload. It further demonstrated that purine catabolism and washout are the mechanisms by which cellular energy substrates are depleted.

In a second bovine study, the impact of depleted high-energy phosphates in border zone myocardium of compensated postinfarct remodeled hearts was examined.[7] Eight pigs were studied 6 weeks after myocardial infarction was induced by ligation of the left anterior descending coronary artery distal to the second diagonal branch. The remote periinfarct region showed modest decreases in ATP and oxidative phosphorylation components, while the zone directly surrounding the infarct (border zone) showed profound abnormalities. In the border zone, ATP concentrations were found to be only 42% of normal, and oxidative phosphorylation components also had decreased. These metabolic defects were independent of a change in mitochondrial concentration, evidenced by preservation of mitochondrial protein concentrations in impacted tissue. These researchers concluded the insufficiency in energy metabolism in the periinfarct region is related to a loss of nucleotides coupled with changes in flux down phosphorylation pathways. This energetic imbalance contributes to the transition from LV remodeling to CHF.

In 16 pigs with LVH secondary to ascending aortic banding with or without resulting development of overt CHF, Ye et al found that myocardial ATP level decreased by 29% in failing hearts.[8] It was also shown that levels of mitochondrial CK concentrations were reduced, forcing a reduction in linear flux. In this model, the severity of the disease correlated with the observation of progressively abnormal high-energy phosphate metabolism. This conclusion was further replicated in a study investigating the role of early energetic insufficiency in the subsequent development of CHF.[9] The 31P-magnetic resonance spectroscopy study in mice showed that metabolic abnormalities strongly correlated with changes in end diastolic volume that developed over time. LaPlace's law confirms that pressure overload increases energy consumption in the face of abnormalities in energy supply. In failing hearts, these energetic changes become more profound as LV remodeling proceeds. It also has been found that similar adaptations occur in the atrium, with energetic abnormalities constituting a component of the substrate for atrial fibrillation in CHF.[10]

LVH is initially an adaptive response to chronic pressure overload, but it is ultimately associated with a 10-fold greater likelihood of subsequent chronic CHF. While metabolic abnormalities are persistent in CHF and LV hypertrophy, at least half of all patients with LVH-associated heart failure have preserved systolic function. This condition is referred to as diastolic heart failure.

Oxidative phosphorylation is directly related to oxygen consumption, which is not decreased in patients with pressure overload LVH.[11] Metabolic energy defects, instead, relate to the absolute size of the energy pool and the kinetics of ATP turnover through oxidative phosphorylation and CK. The deficit in ATP kinetics is similar in both systolic and diastolic heart failure and may be both an initiating event and a consequence. Inadequate ATP availability would be expected to initiate and accentuate the adverse consequences of abnormalities in energy-dependent pathways. Factors that increase energy demand, such as adrenergic stimulation and biochemical remodeling, exaggerate the energetic deficit. Consequently, the hypertrophied heart is more metabolically susceptible to stressors such as increased chronotropic and inotropic demand and ischemia.

In humans, this metabolic deficit is shown to be greater in compensated LVH (with or without concomitant CHF) than in dilated cardiomyopathy, with changes in energetics shown to reach 30% vs 10% to 20% and relative rates of CK flux reduced by 65% vs 50% in LVH and dilated cardiomyopathy, respectively.[12,13] Hypertensive heart disease alone was not shown to contribute to alterations in high energy phosphate metabolism, but it can contribute to LVH and diastolic dysfunction that can later affect cardiac energetics.[14,15] Further, for a similar clinical degree of CHF, volume overload hypertrophy does not induce significant high-energy phosphate impairment, but pressure overload does.[16]

Type 2 diabetes also has been shown to contribute to altering myocardial energy metabolism early in the onset of diabetes, and these alterations in cardiac energetics may contribute to LV functional changes.[17] The effect of age on progression of energetic altering also has been reviewed, with results of both human[18] and

animal[19] studies suggesting that increasing age plays a moderate role in the progressive changes in cardiac energy metabolism that correlates to diastolic dysfunction, LV mass, and ejection fraction.

Cardiac energetics also provide important prognostic information in patients with heart failure, and determining the myocardial contractile reserve has been suggested as a method of differentiating which patients would most likely respond to cardiac resynchronization therapy (CRT) seeking to reverse LV remodeling. In a study involving 31 patients with CHF and nonischemic cardiomyopathy, Ypenburg et al determined that patients showing positive contractile reserve, as evidenced by an increase in ejection fraction of greater than 7% when stimulated by low-dose dobutamine infusion, were most likely to respond to CRT and reverse remodeling of the left ventricle.[20] Nonresponders showed a negative contractile reserve, suggesting increased abnormality in cardiac energetics.

Taken together, results of clinical and laboratory studies confirm that energy metabolism in CHF and LVH is of vital clinical importance. To summarize, cardiac energy metabolism is a complex and often misunderstood process. Energy substrates must be maintained to keep the ATP pool at optimum levels. In diseased hearts, dysfunctional energy is the norm. Therefore, any intervention that will slow the rate of ATP degradation and/or speed up recovery will minimize damage and enhance cardiac function. Treatment options that include metabolic intervention with therapies shown to preserve energy substrates or accelerate ATP turnover are indicated for at-risk populations or patients at any stage of disease.

ENERGY NUTRIENTS FOR CONGESTIVE HEART FAILURE
D-Ribose (Ribose)

The preservation of ATP is vital in the heart, especially during bouts of ischemia, as a reduction in ATP level corresponds to a loss of diastolic function. The administration of ribose supports purine synthesis and salvage pathways promoting diastolic function (Figure 5).

The effect of the pentose monosaccharide, D-ribose, in cardiac energy metabolism has been studied since the 1970s, with clinical studies describing its value as an adjunctive therapy in ischemic heart disease first appearing in 1991. Ribose is a naturally occurring simple carbohydrate that is found in every living tissue, and natural synthesis occurs via the oxidative pentose phosphate pathway of glucose metabolism. But the poor expression of gatekeeper enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase limit its natural production in heart and muscle tissue. The primary metabolic fate of ribose is the formation of 5-phosphoribosyl-1-pyrophosphate (PRPP) required for purine synthesis and salvage via the purine nucleotide pathway. PRPP is rate limiting in purine synthesis and salvage, and concentration in tissue defines the rate of flux down this pathway. In this way, ribose is rate-limiting for preservation of the cellular adenine nucleotide pool.

As a pentose, ribose is not used by cells as a primary energy fuel. Instead, ribose is preserved for the important metabolic
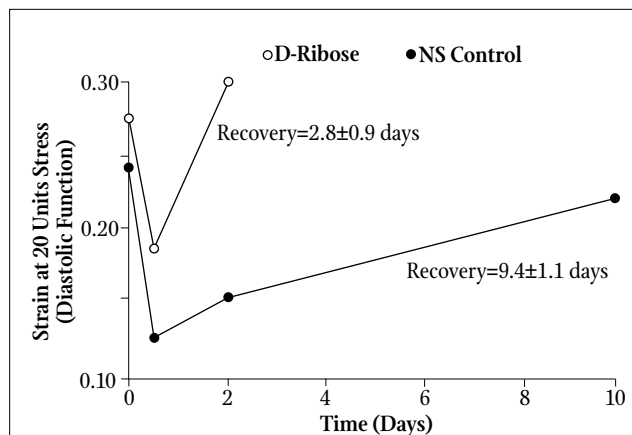
FIGURE 5. Replacing lost energy substrates through the *de novo* pathway of energy synthesis begins with D-ribose (D-ribose-5-phosphate). D-ribose is also critical to adenine nucleotide "salvage" reactions, capturing AMP degradation products before they can be washed out of the cell. The administration of D-ribose corresponds to an increase in diastolic function. Adapted with permission from Tveter K. *Pediatr Res*. 1988;23:226A.

task of stimulating purine nucleotide synthesis and salvage. Approximately 98% of consumed ribose is quickly absorbed into the bloodstream and is circulated to remote tissue with no first-pass effect by the liver. As ribose passes through the cell membrane, it is phosphorylated by membrane-bound ribokinase before entering the pentose phosphate pathway downstream of the gatekeeper enzymes. In this way, administered ribose is able to increase intracellular PRPP concentration and initiate purine nucleotide synthesis and salvage.

The study of ribose in CHF was first reported in the *European Journal of Heart Failure* in 2003.[21] Until that time, the clinical benefit for ribose in cardiovascular disease was largely confined to its increasing role in treating coronary artery disease and other ischemic heart diseases, where its benefit has been well established. The reported double-blind, placebo-controlled, crossover study included patients with chronic coronary artery disease and New York Heart Association (NYHA) Class II/III CHF. Patients underwent 2 treatment periods of 3 weeks each, during which either oral ribose (5 g 3 times daily) or placebo (glucose; 5 g 3 times daily) was administered. Following a 1-week washout period, the alternate test supplement was administered for a subsequent 3-week test period. Before and after each 3-week trial period, assessment of myocardial function was made by echocardiography, and the patient's exercise capacity was determined using a stationary exercise cycle. Participants also completed a quality-of-life questionnaire. Ribose administration resulted in significantly enhanced indices of diastolic heart function and exercise tolerance and was also associated with improved quality-of-life score. By comparison, none of these parameters was changed with glucose (placebo) treatment.

In addition to impaired pump function, CHF patients exhibit compromised ventilation and oxygen uptake efficiency that presents as dyspnea. Ventilation efficiency slope and oxygen

uptake efficiency slope are highly sensitive predictors of CHF patient survival that can be measured using submaximal exercise protocols that included pulmonary assessment of oxygen and carbon dioxide levels. In one study, ribose administration (5 g 3 times daily) to NYHA Class III/IV CHF patients significantly improved ventilation efficiency, oxygen uptake efficiency, and stroke volume as measured by oxygen pulse.[22]

A second study showed that in NYHA Class II/III CHF patients ribose administration significantly maintained VO_{2max} when compared to placebo and improved ventilatory efficiency to the respiratory compensation point.[23] A third similar study involving patients with NYHA Class III CHF patients investigated the effect of ribose on Doppler Tei Myocardial Performance Index (MPI), VO_{2max}, and ventilatory efficiency, all powerful predictors of heart failure survival in a Class III heart failure population.[24] Results showed that ribose improved MPI and ventilatory efficiency while preserving VO_{2max}. Results of these studies show that ribose stimulates energy metabolism along the cardiopulmonary axis, thereby improving gas exchange.

Increased cardiac load produces unfavorable energetics that deplete myocardial energy reserves. Because ribose is the rate-limiting precursor for adenine nucleotide metabolism, its role in preserving energy substrates in remote myocardium following infarction was studied in a rat model.[25] In this study, male Lewis rats received continuous venous infusion of ribose or placebo via an osmotic mini-pump for 14 days. The animals underwent ligation of the left anterior descending coronary artery 1 to 2 days after pump placement to produce an anterior wall myocardial infarction. Echocardiographic analysis performed preoperatively and at 2 and 4 weeks after infarction was used to assess functional changes as evidenced by ejection indices, chamber dimensions, and wall thickness.

By all 3 measured indices, ribose administration better maintained the myocardium. Contractility and wall thickness were increased, and less ventricular dilation occurred. This study showed that the remote myocardium exhibits a significant decrease in function within 4 weeks of myocardial infarction, and that, to a significant degree, ribose administration prevents this dysfunction. It was also revealed that increased workload on the remote myocardium affects cardiac energy metabolism, which results in lower myocardial energy levels. Elevating cardiac energy level improves function and may also delay chronic vulnerable changes in a variety of CHF conditions.

The therapeutic advantage ribose provides in CHF suggests its value as an adjunct to traditional therapy for this disease. Researchers and practitioners using ribose in cardiology practice recommend a dose range of 10 g/day to 15 g/day as metabolic support for CHF or other heart disease. Patients are placed on the higher dose following a regimen of 5 g 3 times daily. If patients respond favorably, a lower dose of 5 g 2 times daily could be tried. Individual doses of greater than 10 g are not recommended because high single doses of hygroscopic carbohydrate may cause mild gastrointestinal discomfort or transient lightheadedness. It is suggested that ribose be administered with meals or mixed in beverages containing a secondary carbohydrate source. In diabetic patients prone to hypoglycemia, it is recommended that ribose be administered in fruit juices.

Coenzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}) increases the turnover of ATP in the inner mitochondrial membrane, which has a positive impact on diastolic function.

CoQ_{10}, or ubiquinone, so named for its ubiquitous nature in cells, is a fat-soluble compound that functions as an antioxidant and coenzyme in the energy-producing pathways. As an antioxidant, the reduced form of CoQ_{10} inhibits lipid peroxidation in both cell membranes and serum low-density lipoprotein and also protects proteins and DNA from oxidative damage. CoQ_{10} also has membrane-stabilizing activity. Its bioenergetic activity and electron transport function for its role in oxidative phosphorylation is probably its most important function.

In CHF, oxidative phosphorylation slows due to a loss of mitochondrial protein and lack of expression of key enzymes involved in the cycle. Disruption of mitochondrial activity may lead to a loss of CoQ_{10} that can further depress oxidative phosphorylation. In patients taking statin-like drugs, the mitochondrial loss of CoQ_{10} may be exacerbated by restricted CoQ_{10} synthesis resulting from HMG-CoA reductase inhibition. Another source of CoQ_{10} deficiency appears in tissues that are highly metabolically active, such as those of the heart, immune system, gingiva, and overactive thyroid gland. Such tissues will benefit from CoQ_{10} support during times of metabolic stress.

Although CoQ_{10} is found in relatively high concentrations in the liver, kidney, and lung, the heart requires the highest levels of ATP activity because it is continually aerobic and contains more mitochondria per gram than any other tissue in the body. Cardiomyocytes, for example, contain almost 5000 mitochondria per cell compared to a biceps muscle cell, which houses approximately 200 mitochondria. Tissue deficiencies and low serum blood levels of CoQ_{10} have been reported across a wide range of cardiovascular diseases, including CHF, hypertension, aortic valvular disease, and coronary artery disease, and research suggests that CoQ_{10} support may be indicated in these disease conditions.[26]

Though the medical literature generally supports the use of CoQ_{10} in CHF, the evaluated dose-response relationships for this nutrient have been confined to a narrow dose range, with the majority of clinical studies having been conducted on subjects who were taking only 90 mg/day to 200 mg/day. At such doses, some patients have responded, and others have not. In 23 controlled trials of supplemental CoQ_{10} in congestive heart failure from 1972 to 2006, 20 showed benefit and 3 failed to show improvement in any significant cardiovascular function.[26,27]

In the well-known study conducted by Permanetter et al, a 100-mg dose of CoQ_{10} failed to show benefit.[28] However, actual blood levels of CoQ_{10} were not obtained in this investigation, and therefore it is impossible to know if a therapeutic blood level was ever achieved. In the second trial by Watson et al, a mean

treatment plasma CoQ_{10} level of only 1.7 µg/mL was obtained with only 2 of the 30 patients having a plasma level greater than 2.0 µg/mL.[29]

A third study, performed by Khatta et al, demonstrated a mean treatment plasma CoQ_{10} level of 2.2±1.1 µg/mL and indicated that approximately 50% of the patients had treatment levels as low as 1.0 µg/mL.[30] Unfortunately, these last 2 clinical trials are frequently quoted as CoQ_{10} failures despite the fact that a biosensitive result was not achieved. In patients with CHF or dilated cardiomyopathy, higher doses of CoQ_{10} in ranges of at least 300 mg or more are necessary in order to get a biosensitive result requiring a blood level of at least 2.5 µg/mL and preferably 3.5 µg/mL.[31] In an analysis in 3 patients with refractory congestive heart failure, such higher doses of CoQ_{10} were required in order to get such a therapeutic result.[32] In a more recent investigation at the Lancisi Heart Institute in Italy, researchers studied 23 patients with a mean age of 59 years, using a double-blind, placebo-controlled, crossover design. Patients were assigned to receive 100 mg of oral CoQ_{10} 3 times daily plus supervised exercise training. The study concluded that CoQ_{10} supplementation improved functional capacity, endothelial function, and LV contractility in CHF without any side effects.[33]

In a previous long-term study of 424 patients with systolic and/or diastolic dysfunction in the presence of CHF, dilated cardiomyopathy, or hypertensive heart disease, a dose of 240 mg/day maintained blood levels of CoQ_{10} above 2.0 µg/mL and allowed 43% of the participants to discontinue 1 to 3 conventional drugs over the course of the study.[34] Patients were followed for an average of 17.8 months, and during that time, a mild case of nausea was the only reported side effect. This long-term study clearly shows CoQ_{10} to be a safe and effective adjunctive treatment for patients with systolic and/or diastolic LV dysfunction with or without CHF, dilated cardiomyopathy, or hypertensive heart disease. These results are further confirmed by an investigation involving 109 patients with hypertensive heart disease and isolated diastolic dysfunction showing that CoQ_{10} supplementation resulted in clinical improvement, lowered elevated blood pressure, enhanced diastolic cardiac function, and decreased myocardial thickness in 53% of study patients.[35]

The effect of CoQ_{10} administration on 32 heart transplant candidates with end-stage CHF and cardiomyopathy was reported in 2004.[36] The study was designed to determine if CoQ_{10} could improve the pharmacological bridge to transplantation, and the results showed 2 significant findings. First, following 6 weeks of CoQ_{10} therapy, the study group showed elevated blood levels from an average of 0.22 mg/L to 0.83 mg/L, an increase of 277%. By contrast, the placebo group measured 0.18 mg/L at the onset of the study and 0.178 mg/L at 6 weeks. Second, the study group showed significant improvement in 6-minute walk test distance, shortness of breath, NYHA functional classification, fatigue, and episodes of waking for nocturnal urination. No such changes were found in the placebo group. These results strongly show that CoQ_{10} therapy may augment pharmaceutical treatment of patients with end-stage CHF and cardiomyopathy.

In a follow-up letter to the editor, I suggested that a new emerging field in "metabolic cardiology" would most likely be realized by those who treat the energy-starved heart at the mitochondrial level.[37] One year later, I addressed that topic in a book, *The Sinatra Solution/Metabolic Cardiology*, in which I recommended magnesium, D-ribose, CoQ_{10}, and L-carnitine as metabolic solutions for any form of cardiovascular disease, especially for those whose quality of life is impaired by CHF and cardiomyopathy.[38]

Levocarnitine (L-carnitine or Carnitine)

L-carnitine plays a significant role in the detoxification pathways in the mitochondria. Such an improvement in shuttling out toxic metabolites enhances the turnover of ATP, thus supporting diastolic function.

Carnitine is derived naturally in the body from the amino acids lysine and methionine. Biosynthesis occurs in a series of metabolic reactions involving these amino acids, complemented with niacin, vitamin B_6, vitamin C, and iron. Although carnitine deficiency is rare in a healthy, well-nourished population consuming adequate protein, CHF, LVH, and other cardiac conditions causing renal insufficiency can lead to cellular depletion and conditions of carnitine deficiency.

The principal role of carnitine is to facilitate the transport of fatty acids across the inner mitochondrial membrane to initiate beta-oxidation. The inner mitochondrial membrane is normally impermeable to activated coenzyme A (CoA) esters. To affect transfer of the extracellular metabolic by-product acyl-CoA across the cellular membrane, the mitochondria delivers its acyl unit to the carnitine residing in the inner mitochondrial membrane. Carnitine (as acetyl-carnitine) then transports the metabolic fragment across the membrane and delivers it to CoA residing inside the mitochondria. This process of acetyl transfer is known as the carnitine shuttle, and the shuttle also works in reverse to remove excess acetyl units from the inner mitochondria for disposal. Excess acetyl units that accumulate inside the mitochondria disturb the metabolic burning of fatty acids. Other crucial functions of intracellular carnitine include the metabolism of branched-chain amino acids, ammonia detoxification, and lactic acid clearance from tissue. Carnitine also exhibits antioxidant and free radical scavenger properties.

Although the role of carnitine in the utilization of fatty acids and glucose in cardiac metabolism has been known for decades, the relationship between carnitine availability in heart tissue, carnitine metabolism in the heart, and carnitine's impact on LV function has been elucidated only recently. Two independent studies have investigated the relationship between tissue carnitine levels and heart function and whether plasma or urinary carnitine levels might actually serve as markers for impaired LV function in patients with CHF.

In the first study of carnitine tissue levels and CHF, the myocardial tissue from 25 cardiac transplant recipients with end-stage CHF and 21 control donor hearts was analyzed for concentrations of total carnitine, free carnitine, and carnitine derivatives. Compared to controls, the concentration of carnitines in the heart muscle of heart transplant recipients was significantly lower, and the level of carnitine in the tissue was directly related to ejection fraction. This study concluded that carnitine deficiency in the heart tissue might be directly related to heart function.[39]

The second study measured plasma and urinary levels of L-carnitine in 30 patients with CHF and cardiomyopathy and compared them to 10 control subjects with no heart disease.[40] Results showed that patients with CHF had higher plasma and urinary levels of carnitine, suggesting that carnitine was being released from the challenged heart muscle cells. Similarly, the results showed that the level of plasma and urinary carnitine was related to the degree of LV systolic dysfunction and ejection fraction, showing that elevated plasma and urinary carnitine levels—indices of carnitines being leached out of compromised cardiomyocyte—might represent measurable physiological markers for myocardial damage and impaired LV function.

A previous investigation examined the effect of long-term carnitine administration on mortality in patients with CHF and dilated cardiomyopathy. This study followed 80 patients with moderate to severe heart failure (NYHA class III/IV) for 3 years. After a 3-month period of stable cardiac function on normal medication, patients were randomly assigned to receive either 2 g of carnitine daily or a matched placebo. After an average of 33.7 months of follow-up, 70 patients remained in the study (33 taking placebo and 37 supplementing with carnitine), and at the end of the study period, 63 had survived (27 placebo and 36 carnitine). This study determined that carnitine provided a benefit to longer-term survival in late-stage heart failure in dilated cardiomyopathy.[41]

A similar placebo-controlled study followed 160 myocardial infarction survivors for 12 months.[42] Eighty subjects were included in each group. The study group received a daily dose of 4 g of L-carnitine; the controls, a placebo. Both the carnitine and control groups continued their conventional therapeutic regimen while on the test substance. Subjects in both groups showed improvement in arterial blood pressure, cholesterol levels, rhythm disorders, and signs and symptoms of CHF over the study period, but all-cause mortality was significantly lower in the carnitine group than in the placebo group (1.2% and 12.5%, respectively). Another double-blind, placebo-controlled trial by Singh et al studied 100 patients with suspected myocardial infarction. Patients taking carnitine (2 g/day for 28 days) showed improvement in arrhythmia, angina, onset of heart failure, and mean infarct size, as well as a reduction in total cardiac events. There was a significant reduction in cardiac death and nonfatal infarction in the carnitine group vs the placebo group (15.6% vs 26%, respectively).[43]

In a European study of 472 patients published in the *Journal of the American College of Cardiology*, 9 g/day of carnitine was administered intravenously for 5 days followed by 6 g/day orally for the next 12 months.[44] The study validated previous findings, demonstrating an improvement in ejection fraction and a reduction in LV size in carnitine-treated patients. Although the European study was not designed to demonstrate outcome differences, the combined incidence of CHF death after discharge was lower in the carnitine group than in the placebo group (6.0% vs 9.6%, respectively), a reduction of more than 30%.

In a 2007 trial, a newer form of carnitine called glycine propionyl L-carnitine (GPLC) demonstrated significant advantages in the production of nitric oxide and lower malondialdehyde (MDA), a marker of lipid peroxidation and oxidative damage. This form of carnitine has demonstrated the important property of vasodilation via nitric oxygen inhibition. GPLC also blocked key steps in the process of platelet aggregation and adhesion, as well as reducing levels of lipid peroxidation and oxidative damage.[45]

SUMMARY

Cardiovascular function depends on the operational capacity of myocardial cells to generate the energy to expand and contract. Insufficient myocardial energy contributes significantly to CHF. Literally, heart failure is an "energy-starved heart."

Although there may be several causes of myocardial dysfunction, the energy deficiency in cardiac myocytes plays a significant role and is probably the major factor in CHF. It is no longer enough that physicians focus on the fluid retention aspects of "pump failure." For instance, diuretic therapies target the kidneys indirectly to relieve the sequelae of CHF without addressing the root cause. Inotropic agents attempt to increase contractility directly yet fail to offer the extra energy necessary to assist the weakened heart muscle. Metabolic solutions, on the other hand, treat the heart muscle cells directly.

We must consider the biochemistry of "pulsation." It is critically important to treat both the molecular and cellular components of the heart when managing CHF. This complexity of cardiac energy metabolism is an often misunderstood phenomenon of vital clinical importance. One characteristic of the failing heart is a persistent and progressive loss of cellular energy substrates and abnormalities in cardiac bioenergetics that directly compromise diastolic performance, with the capacity to impact global cardiac function. Cardiologists must learn that the heart is all about ATP, and the bottom line in the treatment of any form of cardiovascular disease, especially CHF and cardiomyopathy, is restoration of the heart's energy reserve. Metabolic cardiology describes the biochemical interventions that can be employed to directly improve energy metabolism in heart cells. In simple terms, sick hearts leak out and lose vital ATP, and the endogenous restoration of ATP cannot keep pace with this insidious deficit and relentless depletion. When ATP levels drop, diastolic function—the most important precursor of congestive heart failure—deteriorates.

D-ribose, L-carnitine, and CoQ_{10} act to promote cardiac energy metabolism and help normalize myocardial adenine nucleotide concentrations. These naturally occurring compounds exert a physiological benefit that directly affects heart function. As the rate-limiting compound, supplemental ribose supports ATP quantity in the synthesis of new ATP. CoQ_{10} and carnitine enhance the turnover of ATP in the inner mitochondrial chain. All are recommended as adjunctive metabolic therapies in the treatment of heart failure and cardiomyopathy. An understanding of this metabolic support for the heart provides the "missing link" that has been eluding cardiologists for decades. Metabolic cardiology offers hope for the future treatment of CHF, cardiomyopathy, and any other form of cardiovascular disease including mitral valve prolapse (frequently a situation involving diastolic dysfunction).

Acknowledgment

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