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Myocardial Ischemia: Alterations in Myocardial Cellular Energy and Diastolic Function, a Potential Role for D-Ribose

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1. Introduction

Cardiovascular disease still remains the leading cause of deaths worldwide in both males and females. A variety of factors have been associated to play a role in the development of this disease, such as an individual's genetic background and continual life style factors. Life style factors (including diet) have greatly influenced the occurrence and progression of this disease. The medical profession has made great efforts to adequately address and to continually stress to their patients an altered life style to confront the non-genetic factors, in order to potentially minimize their risk for cardiovascular disease. This campaign has centered on a continual direction for refinements in diet, regular exercise, smoking cessation, and to control blood pressure to lower their risk for cardiovascular disease.

The World Health Organization has reported that approximately 17 million people die of cardiovascular diseases, including myocardial infarcts and strokes, every year. [1] The most common type of cardiovascular disease is atherosclerosis, which has shown to progress overtime. This progression involves the narrowing of our arteries, which ultimately limits the delivery of oxygen to viable tissue beds. [2] Atherosclerosis is not confined to a sole anatomic region; for it can eventually progress to involve many arterial vessels in our circulation, producing not only heart disease, but cerebrovascular and peripheral vascular devastating pathological sequelae. Financially, cardiovascular diseases have taxed economies and current trends have shown its continued burden on healthcare dollars worldwide.

The progression of coronary arterial atherosclerosis has the potential to eventually produce myocardial ischemia, reflected in clinical symptoms of angina or chest pain. This atherosclerotic state produces a decrease in blood flow to the myocardium, producing a decrease availability of oxygenated blood to these muscular regions of the heart. Clinically, patients afflicted with coronary artery disease/myocardial ischemia can experience symptoms of angina or chest pain, commonly during and following stressful situations; however, some unfortunately can even have episodes at rest. Furthermore,

with the progression of coronary artery disease and the development of significant coronary arterial atherosclerosis, patients are susceptible of sustaining an acute myocardial infarction or live with a chronic, debilitating condition, which has the potential of advancing into the development of heart failure.

Along with significant myocardial ischemic coronary arterial disease, many patients can experience functional abnormalities, such as diastolic dysfunction or an abnormality in ventricular relaxation. This ventricular dysfunctional condition has continued to be a challenging clinical problem for physicians because as of today, there is not yet an approved effective, solely directed therapy for myocardial diastolic dysfunction. Current medical investigations have found that left ventricular diastolic dysfunction is more prevalent than expected. Redfield et al. reported in 2042 randomly selected adults over the age of 45 that 21% had mild and 7% had at least moderate diastolic dysfunction. Six percent had moderate or severe diastolic dysfunction with a normal ejection fraction. [3] This has been supported by additional published studies that have shown that diastolic dysfunction exists with its prevalence varying with age. Fischer et al. found diastolic dysfunction in 2.8% of individuals between 25-35 years of age and increasing to 15.8% among those older than 65 years of age. Compared to women, men had a higher rate of diastolic abnormalities (13.8% vs. 8.6%). Factors associated with diastolic abnormalities have included arterial hypertension, evidence of left ventricular hypertrophy and coronary artery disease. Additionally, diastolic dysfunction has been related to a higher body mass index, high body fat and diabetes mellitus. [4] Unfortunately, when diastolic dysfunction develops early in the post myocardial infarction clinical period, these patients tend to have a poorer outcome.

Myocardial ischemia is a common entity in the development of congestive heart failure (CHF) and many of these patients will have a component of diastolic dysfunction. Clinically, at least half of patients diagnosed with CHF will have a degree of diastolic dysfunction solely or in combination with systolic dysfunction. These CHF patients with diastolic dysfunction can have a challenging therapeutic course and a less favorable clinical outlook. Ingwall and Weiss proposed that the failing heart is energy starved. However, this theory is not novel. This theory was previously proposed, but was not actively pursued because it was unclear whether ATP levels really decreased and if these levels did decrease in the failing heart, then the remaining pool of ATP compounds should be sufficient to satisfy myocardial ATP-requiring reactions. [5] Currently, there appears to be renewed interest in this hypothesis; that the failing heart is energy starved. The advancement in biophysical tools, such as nuclear magnetic resonance (NMR) spectroscopy and positron emission tomography (PET) scans have aided in providing a better understanding of this myocardial energy/functional relationship.

2. Cellular energy and function during and following myocardial ischemia: A potential role for D-ribose

2.1 Pre-clinical investigations

All cells require high energy phosphates, predominantly ATP, to maintain their integrity and function. Normally, the cellular supply of ATP meets tissue demands. Glycolysis and

the tricarboxylic acid cycle pathways produce ATP compounds with glucose as the starting substrate. However, cells can also rely on alternative pathways, such as the hexose monophosphate shunt or pentose phosphate pathway for the production of energy molecules. [6] As stated, the supply of ATP is essential to preserve cellular cardiac energy and function; and without these levels of ATP, a myocyte's integrity and function is jeopardized. When myocytes are subjected to ischemia, there is a depletion in energy stores, which can potentially decrease intracellular reactions, including cellular function. Obviously, if this ischemic insult is severe enough, viability can be affected. Besides this assumed immediate depletion in ATP levels, numerous studies have shown that this depletion in myocardial ATP levels from ischemia lasts for a considerable time period due to slow adenine nucleotide synthesis, of which this delay in ATP recovery is reflected in abnormal function. [7] Because of these published findings, future developed methods directed at enhancing the recovery of this energy deficiency due to ischemia should strongly be considered in the therapeutic management of myocardial ischemic diseases.

There is a direct interaction between adequate myocardial ATP levels and the development of ventricular dysfunction, predominantly diastolic dysfunction. Calcium plays a major role in this interaction, which is an energy dependent process. Adenosine triphosphate provides the energy for this interaction between cytosolic calcium and the sarcoplasmic reticulum. Depleted ATP levels can result in calcium remaining fixed to troponin longer in diastole, producing a state of diastolic dysfunction or altered ventricular compliance. Following ischemia, a return in diastolic function may be limited by the availability of the high energy phosphate, ATP. [8] Theoretically, efforts to maximize the recovery of myocardial ATP levels during and following ischemia could aid in minimizing the functional untoward effects following ischemia.

Research over decades has explored the relationship of myocardial ATP levels during and following ischemia. Most of these initial myocardial ischemic studies involved acute isolated heart models, mainly Langendorff or Neely preparations. Reibel and Rovetto reported in isolated perfused rat hearts that a moderate ischemic insult (10-30 minutes) resulted in a 50-70% decrease in myocardial ATP levels. [9] The recovery of myocardial ATP levels following ischemia is not prompt with reperfusion. Hours to days are required for substantial recovery, depending upon the degree of the ischemic insult. Kloner et al. found that the recovery of ATP compounds after 15 minutes of coronary occlusion in the healthy canine heart was only 75% restored after three days with one week required for full recovery. [10] Likewise, Zimmer concurred that an extended time period is required for the recovery of depressed myocardial energy levels, as well as a measured improvement in the alteration in mechanical function following ischemia. [11] Even though these isolated myocardial experimental models have provided important findings, they have limitations due to the nature of the isolated heart preparation. Therefore, experiments involving an intact animal model would be essential to support these initial isolated heart preparation findings. Short term investigations involving an intact animal model found similar findings in measured myocardial adenine nucleotide levels following ischemia. Twelve to 30 minutes of myocardial ischemia produced a substantial drop in ATP levels with a significant decrease in total adenine nucleotides, and days were required for total recovery. [12]

However, to fully appreciate this important energy-functional relationship, a chronic animal model to measure both myocardial energy levels and function would be ideal to better understand the long term effects of ischemia. A chronic canine animal model was developed to provide the means for long term assessment of myocardial energy levels and function during and following ischemia. [13-15] Using this chronic model, 20 minutes of normothermic myocardial ischemia produced a significant decrease (approximately 50%) in ATP levels, which was accompanied with a state of left ventricular diastolic dysfunction. Furthermore, the data from this chronic animal study confirmed that the effects of myocardial ischemia have a long term effect. Researchers reported that there was a substantial delay, over one week, in myocardial energy levels and functional recovery following a moderate, reversible ischemic insult. [13-15]

Ward et al. reported that myocardial precursor availability is an important limiting factor in the recovery of myocardial ATP molecules following an ischemic insult. [15] Many researchers have investigated various substrates and methods in replenishing depressed levels of ATP following ischemia. Investigations with adenine nucleotide precursor substrates have included adenosine, 5-amino-4-imidazolecarboxamide riboside, inosine, adenine, D-ribose, as well as an adenine degradative enzymatic inhibitor (erythro-9-(2-hydroxy-3-nonyladenine hydrochloride). However, these studies have reported mixed results in the recovery of energy molecules and function following ischemia. The majority of these precursors have at best shown a minimal improvement in both ATP recovery and function. However, this was not the case when investigating the effects of D-ribose during and following myocardial ischemia. D-ribose, a natural occurring pentose carbohydrate, supplementation demonstrated in numerous animal studies its significant benefit in enhancing the return in ATP levels and improved function following global and regional myocardial ischemia. Zimmer and Gerlach reported that supplementation with D-ribose in adult, isolated rat hearts resulted in an increase rate of adenine nucleotide synthesis. [16] Pasque et al. found similar results in isolated, perfused, working rat hearts subjected to 15 minutes of ischemia, followed by 2-15 minutes of myocardial work. D-ribose supplementation improved the recovery in myocardial ATP levels along with a mean percent improvement in functional recovery. [17] St. Cyr et al. also observed the benefits of D-ribose and adenine in a chronic animal model. Supplementation with D-ribose and adenine following 20 minutes of global ischemia resulted in 85% return in ATP levels as compared to no ATP recovery without D-ribose and adenine. [18]

In the same chronic canine model design described by St.Cyr et al. with additional functional instrumentation, Schneider et al. reported similar ATP benefits with D-ribose and adenine, as well as improvements in left ventricular non-compliance/diastolic dysfunction following 20 minutes of global myocardial ischemia. [13,19] Further investigations revealed the sole benefits of D-ribose during and following ischemia. Tveter et al. investigated the benefits of D-ribose alone in a chronic canine model, in which hearts were subjected to a moderate (20 minutes) global myocardial ischemic insult. They found that D-ribose solely produced similar benefits in both myocardial energy levels and functional recovery following global ischemia, as was previously reported with D-ribose and adenine. [20] D-ribose appeared to solely enhance the recovery of myocardial adenine nucleotide levels, improve diastolic dysfunction and the adenine nucleotide pool following ischemia.

A significant restrictive or narrowing of a coronary arter(ies) can potentially result in an acute occlusion or an acute myocardial infarct, for which myocardial dysfunction post infarct can be present. Following infarction, some of these hearts can experience a continual decline in function, leading to the development of heart failure. The remote myocardium not involved in the infarcted tissue is subjected to an increased workload, which can severely tax its myocardial energy supply, which over time can affect remodeling. Zimmer et al. reported in adult rats that a decline in left ventricular hemodynamics occurs following myocardial infarction. They observed a progressive decline in left ventricular systolic pressure, a decline in left ventricular dP/dt_{max}, elevated left ventricular end diastolic pressure, and lower cardiac outputs and stroke volume indices post infarction. Upon supplying the substrate D-ribose, there was an improvement in the above measured left ventricular hemodynamic parameters with stimulation in adenine nucleotide synthesis. [21] Likewise, Befera et al. observed similar findings with the supplementation of D-ribose following acute myocardial infarction in adult rats. They found an improvement in left ventricular function in the remote left ventricular areas when supplying D-ribose. There was increased contractility and myocardial wall thickness with less ventricular dilatation with D-ribose supplementation. [22]

These two pre-clinical, animal studies reported that D-ribose prevented or delayed the development of left ventricular dysfunction following acute myocardial infarction. Hence, the question posed is: might D-ribose offer an additional benefit, if supplemented prior to a myocardial infarction? When D-ribose was supplied pre-infarction, Gonzalez et al. reported that providing D-ribose in adult rats resulted in a significant reduction in the created left ventricular infarct area and a significant improvement in left ventricular function when assessed at 6 hours post infarct. Left ventricular systolic pressure and contractility were restored to normal levels with a significant improvement in measured parameters of left ventricular relaxation with supplemental D-ribose. [23]

2.2 Clinical D-ribose evaluation

The observed positive energy enhancing and functional benefits associated with D-ribose in the pre-clinical investigations initiated subsequent clinical studies to further assess its potential in patients afflicted with cardiovascular diseases. Because of the benefits of D-ribose during and following ischemia, researchers investigated this potential in enhancing the identification of hibernating myocardium. Hibernating myocardium represents regional areas of myocardial dysfunction due to prolonged hypoperfusion or ischemia. This condition can be reversed upon restoration of a more adequate level of blood flow to these regions. Theoretically, efforts to aid in the identification of these regions can help in the management strategies for revascularization. Current methods in identifying these regions include Thallium-201 scans, dobutamine stress echocardiography, PET, and magnetic resonance imagery. Hibernating myocardium is likely to be associated with lower levels of myocardial ATP; and therefore, supplementation with an adenine nucleotide agent might aid in further identifying these viable regions. D-ribose has demonstrated a benefit in this identification process. Before undertaking clinical investigations, pre-clinical animal studies demonstrated the identification benefit of D-ribose in hibernating myocardium. In the clinical realm, Perlmutter et al. reported that D-ribose identified more reversible defects

using Thalium-201 scans. [24] Other clinical studies have supported this finding. Hegewald et al. found that D-ribose also increased the detection of viable ischemic myocardial regions using SPECT Thallium imaging. [25] More recently, Sawada et al. demonstrated that the supplementation of D-ribose provided anti-ischemic effects with improving the identification of wall motion dysfunctional abnormalities during dobutamine stress echocardiography. [26]

Previously reported positive pre-clinical animal studies demonstrating the benefits of D-ribose during and following ischemia generated additional clinical investigative interest. Since D-ribose has shown in animal studies to enhance the recovery in ATP levels and improve function following myocardial ischemia, Pliml et al. argued that there is significant impairment in ATP levels in the ischemic myocardium. The current lack of therap(ies) directed to the restoration or preventing further decrease in these myocardial energy compounds lead the researchers to design a study in which patients with stable coronary artery disease underwent serial treadmill exercise testing while supplementing with D-ribose. D-ribose demonstrated significant benefits in increasing treadmill exercise time before the onset of angina and/or ischemic electrocardiographic changes. [27]

Myocardial ischemia is an etiological factor in the development of CHF and reports have proposed that the failing heart is energy starved. [5] Because of D-ribose's ability to enhance the recovery of myocardial ATP levels and improve diastolic dysfunction following ischemic, Omran et al. investigated the role of D-ribose in class II-III CHF patients. They reported both objective and subjective benefits with D-ribose. There was an improvement in diastolic dysfunctional parameters, as assessed by serial echocardiographic examinations; and subjectively, the patients experienced an improved quality of life and physical function. [28]

Commonly, CHF patients complain of shortness of breath and fatigue. As their failure progresses, patients have a decrease in their ventilatory efficiency. Carter et al. found that supplementation with D-ribose enabled class II-III CHF study patients with left ventricular dysfunction to maintain their VO_{2max}, improve their ventilatory efficiency and experience a positive trend in their daily quality of life assessment. [29] Vijay et al. concurred in a separate clinical study the positive benefits of D-ribose in class II-IV CHF patients. They observed significant improvements in ventilatory efficiency in class III-IV patients with a positive, but not statistically significant, .trend in improved ventilator efficiency in class II patients. [30]

The use of D-ribose has also been explored in cardiovascular surgery. Alterations in myocardial function have been observed in the post-ischemic interval following surgery. Wyatt et al. found that the use of a cardioplegic solution containing adenosine, hypoxanthine and D-ribose during intra-operative ischemia maintained myocardial energy levels during ischemia and with reperfusion resulted in enhanced functional recovery post operatively. [31] Vance et al. reported that parenteral use of D-ribose in patients undergoing elective aortic valve replacement with or without accompanying coronary arterial bypass grafting resulted in the maintenance in ejection fraction postoperatively, unlike the decline in ejection fraction observed in the patients not receiving D-ribose. They concluded that the treatment regimen of D-ribose preserved left

ventricular function peri-operatively. [32] More recently, oral D-ribose was added to a metabolic designed protocol for patients undergoing off pump coronary artery bypass revascularization procedures. Perkowski et al. found that this D-ribose metabolic protocol resulted in lower mortality and morbidities, along with a significant early postoperative improvement in cardiac index in patients undergoing "off pump" coronary artery revascularization. [33]

3. Summary

Even with the advances in cardiovascular medical technologies over decades, cardiovascular disease still ranks as the leading cause of death worldwide for both males and females. Myocardial ischemia, a factor in cardiovascular disease, has continued to be a leading cause of deaths in middle to elderly aged individuals. With continued current aggressive education, there have been strides in addressing the cardiovascular risk factors in this disease, including refinements in diet, regular exercise, smoking cessation, and blood pressure control. However, the underlying metabolic energy deficiency found with myocardial ischemia still requires further attention.

Every cell requires adequate levels of high energy phosphates, i.e. ATP, to maintain its integrity and function. Myocardial ischemia lowers myocardial ATP levels, which has shown to reflect functional abnormalities. Relaxation of the myocardium, occurring during diastole, requires adequate ATP levels for the normal flux of calcium interacting with the sarcoplasmic reticulum. Without adequate levels of myocardial ATP, a state of ventricular diastolic dysfunction or non-compliance develops. Over decades research has centered on developing strategies in replenishing deficient levels of ATP during and following myocardial ischemia. The abundance of research has entertained on providing metabolic substrates to regenerate ATP compounds following ischemia. The results of these numerous investigations have been mixed; however, supplementation with D-ribose, a natural occurring pentose carbohydrate, has been found to not only to enhance the recovery of ATP levels, but to aid in improving the state of ventricular diastolic dysfunction following myocardial ischemia. D-ribose has shown to improve ventricular compliance following ischemia, for which there is not an approved marketed device or pharmaceutical that can offer this functional benefit.

The clinical therapeutic cardiovascular uses of D-ribose continue to expand. Published studies have reported its potential benefits, such as in acute and chronic myocardial ischemic conditions, identifying hibernating myocardium, in CHF patients, and its use in the peri-operative cardiovascular surgical patient. The literature has provided support that supplemental D-ribose may offer the means to enhance the recovery of myocardial cellular energy with functional benefits in patients afflicted with ischemic cardiovascular disease.

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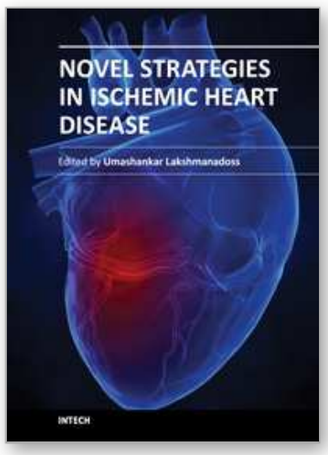

Novel Strategies in Ischemic Heart Disease

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The first edition of this book will provide a comprehensive overview of ischemic heart disease, including epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic tests, differential diagnosis, treatment, complications and prognosis. Also discussed are current treatment options, protocols and diagnostic procedures, as well as the latest advances in the field. The book will serve as a cutting-edge point of reference for the basic or clinical researcher, and any clinician involved in the diagnosis and management of ischemic heart disease. This book is essentially designed to fill the vital gap existing between these practices, to provide a textbook that is substantial and readable, compact and reasonably comprehensive, and to provide an excellent blend of "basics to bedside and beyond" in the field of ischemic heart disease. The book also covers the future novel treatment strategies, focusing on the basic scientific and clinical aspects of the diagnosis and management of ischemic heart disease.

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