The Patented Uses of D-Ribose in Cardiovascular Diseases

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Abstract: Cardiovascular diseases account for more deaths worldwide than any other illness. Myocardial ischemia, a common finding in cardiovascular diseases, lowers cellular energy levels, which affects a cell's integrity and function. Pre-clinical animal studies have reported lower cellular energy levels with an associated decreased function following myocardial ischemia. Recently, scientists have reported that the failing heart is energy starved and yet no pharmaceuticals have been able to address this issue with satisfactory results. Over decades, researchers have explored the use of various metabolites to replenish deficient cellular energy levels following induced ischemia with mixed results. However, D-ribose, a natural occurring carbohydrate, has demonstrated significant enhancing abilities in replenishing deficient cellular energy levels following myocardial ischemia, as well as improving depressed function in numerous animal investigations. Subsequent clinical trials have further substantiated these benefits of D-ribose in patients afflicted with ischemic cardiovascular disease and those carrying the diagnosis of congestive heart failure. The future of effective therapies for ischemic heart disease and congestive heart failure must strongly consider novel pharmaceuticals directed at replenishing cellular energy levels. Intellectual property and the represented patents in this paper emphasize the use of D-ribose for its cellular energy enhancing potential, reflected in both objective and subjective clinical improvements; therefore, substantiating its value in patients with ischemic cardiovascular diseases.

Keywords: Cardiovascular diseases, myocardial ischemia, congestive heart failure, D-ribose, energy, function, quality of life & therapeutic benefits.

INTRODUCTION

Cardiovascular disease still ranks as the leading cause of deaths worldwide with myocardial ischemia a common etiological factor. Myocardial ischemia produces lower cellular levels of adenosine triphosphate (ATP), a key energy molecule important to all cells. Adequate ATP levels are important for the maintenance of a cell's integrity and function. Decreased cellular ATP levels found in ischemic vascular diseases have been widely known, but not until recently has attention focused on the importance of this deficient cellular energy state in cardiovascular diseases. Historically, cellular energy depletion in cardiac myocytes during stress was described decades ago [1], and yet no current therapies have addressed this altered metabolic state.

The incidence of congestive heart failure (CHF) continues to escalate, for which palliative therapies exist. Ingwall and Weiss proposed that the failing heart is energy starved, which has been further supported by others [2, 3]. Since adequate cellular energy levels are necessary to maintain integrity and function, this decrease energy state can play a major role in the heart's function. Underlying mechanism(s) accounting for the development and progression of CHF include either ventricular diastolic or systolic dysfunction alone or in combination. Many clinicians feel that the awareness of myocardial dysfunction may be underestimated. Redfield *et al*. reported that approximately 20% of individuals over the age of 40 are at risk of developing heart failure during their lifetime [4].

The therapeutic challenge in assessing and treating CHF patients with diastolic dysfunction resides in relieving symptoms and improving quality of life. Conventional therapies have focused on the clinical management of lowering systolic and diastolic blood pressure, control of ventricular rate for atrial fibrillation, and decrease cardiovascular volume overload [5], all of which have limitations. Furthermore, current palliative therapies can and do have a financial burden on a country's economy. In the United States there are more than 550,000 newly diagnosed CHF patients/year with over 5 million patients currently afflicted this with disease and approximately 52,000 annual deaths. Approximately 3.1 million hospital admissions occur each year, costing over $23 billion [6]. The constant yearly increases in CHF patients further taxes health care dollars in both the acute and chronic care settings. The goal in treating CHF needs to refine current pharmaceuticals, nurture novel agents or methods to aid in improving patient care, quality of life measures, and lessen the financial burden on societies.

Pharmaceutical agents direct their action in relieving symptoms to improve a patient's quality of life, and possibly lessening the progression of disease. This is not always the case, for many patients experience worsening symptoms, which leads to administrating increasing dosages of their current medications, potentially adding other class pharmaceuticals, in order to slow the progression in their disease. Changes in pharmaceutical management have the potential to produce new or more pronounced undesirable

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side effects, further affecting daily compliance. When new and even less desirable side effects arise, many patients seek alternative therapeutic options, including device-related technologies and/or nutraceutical supplements [7, 8]. This attraction to alternative therapies has increased and initial clinical studies have shown clinical benefits even with continued reservations by traditional physicians.

ADENOSINE TRIPHOSPHATE LEVELS

Adenosine triphospate levels are important for the maintenance of a cell's homeostasis, including integrity and function. For example, adequate intracellular ATP levels are critical for the normal relationship between calcium and the sarcoplasmic reticulum, necessary for the maintenance of myocardial function [9]. Low levels of ATP can produce ventricular diastolic dysfunction. Pre-clinical investigations involving canines subjected to 20 minutes of reversible myocardial global ischemia reported lower ATP levels with an accompanying state of diastolic dysfunction and complete recovery required more than 9 days due to slow adenine nucleotide synthesis [10]. At present there are no therapies that are effective at improving diastolic dysfunction; however, research interest in this entity continues and future therapies directed at improving diastolic dysfunction should focus at preserving, or if needed, replenishing myocardial ATP molecules. Furthermore, besides of the known patients afflicted with diastolic dysfunction, there are asymptomatic individuals with unknown cardiac diastolic functional abnormalities as reported by Redfield *et al.* [4] for which there is a need not only treat their undiagnosed condition, as well as to potentially minimize disease progression.

METABOLIC ENERGY SUPPLEMENTATION

Adenosine triphosphate recovery depends on increased levels of phosphoribosyl-pyrophosphate (PRPP), which is formed from ribose-5-phosphate by the enzyme ribose-phosphate diphosphokinase. Increased levels of PRPP can aid in the production of ATP and increase the adenine nucleotide pool. Researchers have investigated various metabolic agents/supplements for their potential in enhancing ATP levels, such as adenosine, 5-amino-4-imidazolecarboxamide riboside, inosine, as well as adenine nucleotide degradative-enzymatic inhibitors [11-13]. The results from many of these investigations have produced mixed results; however, D-ribose, a natural occurring pentose carbohydrate, has shown remarkable promise. D-ribose is a key carbohydrate in many intracellular processes, a major component in the energy ATP molecule itself and plays an important role in both RNA and DNA synthesis. Supplementation of D-ribose during and following myocardial ischemia has shown to significantly regenerate ATP levels by being unique in bypassing rate-limiting enzymatic steps in the pentose phosphate pathway (PPP), leading to increased cardiac PRPP levels and adenine nucleotide biosynthesis [14-16].

Past and current investigations have demonstrated the importance of D-ribose in replenishing deficient cellular levels of ATP and in improving ventricular relaxation, key in patients afflicted with ischemic heart disease and CHF. The appreciation that myocardial ischemia and the failing heart is reflected in lower levels of adenine nucleotides and with the benefits discovered with D-ribose, a future direction by pharmaceutical companies should consider developing agents for these energy deficient disease states.

D-RIBOSE METABOLISM

D-ribose is rapidly absorbed and enters the PPP for purine and pyrimidine nucleotide biosyntheses or converted into glycolytic intermediates. Between 88-100% of oral D-ribose is readily absorbed from the gastrointestinal tract with little first-pass hepatic metabolism. Studies have shown that even at very high doses, only a small amount appears unchanged in the urine [17]. D-ribose has been determined to be safe with few adverse side effects, even when infused at rates as high as 222 mg/kg/hr as reported by Gross *et al*. in human subjects [18]. Sub-chronic toxicology and embryotoxicity/teratogenicity studies in rodents have reported no significant gross or histological abnormalities even with oral consumption up to 20% of their daily diet [19, 20]. However, oral and parenteral D-ribose supplementation can produce a transient lowering in serum glucose levels and when dextrose is added with D-ribose, this transient hypo-glycemic interval found with D-ribose alone is alleviated. Orally, D-ribose is slightly sweet and bolus doses exceeding 200 mg/kg/hr have reported the occurrence of a variety of gastrointestinal symptoms, such as occasional nausea, loose stools and rarely incidences of diarrhea. These gastrointestinal disturbances vary with each individual.

PRE-CLINICAL INVESTIGATIONAL STUDIES

Pre-clinical animal studies have demonstrated the safety and benefits of D-ribose in replenishing deficient myocardial ATP levels with an associated improvement in ventricular function. These studies have included acute isolated heart preparations and both acute and chronic *in vivo* investigations. Benefits in the regeneration of ATP and the improvement in physiological parameters have been well documented [21-23]. Animal investigations have also reported that unlike the lengthy energy and functional recovery time that normally occurs following reversible myocardial ischemia, D-ribose substantially shortens this time interval [14], along with an improvement in ventricular function [23]. The myocardial functional benefits observed with D-ribose in these animal studies, generated clinical investigations in patients afflicted with cardiovascular diseases, such as ischemic heart disease and CHF.

CLINCAL EVALUATIONS

Clinically, the potential benefits of D-ribose have been investigated in many cardiovascular diseases. Pliml *et al*. claimed that myocardial ischemia produces lower levels of myocardial ATP, abnormal findings during exercise and current therapeutics have not addressed this metabolic deficient state. To assess this premise, twenty male patients with stable ischemic, coronary artery disease underwent treadmill exercise assessments in a double blind study using supplemental oral D-ribose or dextrose for 5 days. D-ribose produced significant benefits by extending their treadmill exercise timed-sessions before developing angina ($p = 0.004$) or objective electrocardiographic changes ($p = 0.002$). Both

of these parameters were non-significant in the placebo arm of the study [24]. The patients in this study were compliant in the D-ribose dose scheduling; however, some patients experienced gastrointestinal problems at these high daily dosages (60gms/day), which may hinder compliance for long term use.

Areas of hibernating myocardium, resulting from decreased coronary blood flow, can create a persistent state of depressed left ventricular function due to chronic ischemia and probably reflects lower levels of myocardial ATP. Numerous researchers have found that the supplementation with D-ribose aids in identifying these regions of hibernation in both animal and human studies. Perlmutter *et al*., in a randomized, placebo control, cross-over trial, reported the use of intravenous D-ribose on Thallium redistribution. Seventeen patients were subjected to two (1 and 2 weeks) Thallium imaging studies during Bruce or modified Bruce exercise tests. Thallium was injected around exercise with planar myocardial imaging. Following exercise either D-ribose or placebo was infused with repeat imaging at 1 and 4 hours. Results revealed that at both 1 and 4 hours of imaging post exercise, D-ribose identified more reversible defects as compared to controls ($p < 0.001$). In another clinical study, Grados-Pizlo *et al*. reported on the effects of D-ribose on hibernating segments during dobutamine stress echocardiography in patients with hibernating myocardium and contractile dysfunction. Twenty-five patients were randomized in a double blind, cross-over trial comparing the effects of D-ribose versus placebo (D_5W) on regional wall motion during dobutamine stress echocardiography. Intravenous D-ribose produced an increase in the frequency of response to dobutamine stress echocardiography ($p = 0.02$). This positive response of these myocardial hibernating segments could have clinical significance for future management strategies involving revascularization [25, 26].

Surgically, the peri-operative benefits of D-ribose have also been observed. The use of D-ribose in aortic valve replacement resulted in preserving left ventricular function peri-operatively. Vance *et al*. reported on twenty patients randomized in a double blind trial, in which eighty percent of patients receiving placebo (D_5W) demonstrated at least a 15% decline at postoperative day 7 ($p = 0.0025$) in ejection fraction after aortic valve replacement; whereas, only 20% of the patients receiving D-ribose showed similar declines ($p = 0.49$) [27]. Furthermore, the peri-operative use of D-ribose in patients undergoing off pump coronary artery bypass procedures has also shown promise. Perkowski *et al.* investigated the role of D-ribose in 207 adult patients undergoing off pump coronary artery bypass. Pre-operative supplementation of D-ribose demonstrated a 36% improvement in cardiac index postoperatively, as compared to only a 13% benefit found in historical controls. Further, this functional benefit with D-ribose was also observed in high risk patients with coronary arterial disease, as well as in patients presenting with acute myocardial infarction [28].

Myocardial ischemia is a major etiological factor for CHF and recent reports have claimed that the failing heart is energy starved [2, 3]. D-ribose can provide a nutrient for enhancing the production of adenine nucleotides in compromised myocardial tissue. Daily doses of oral D-ribose have shown significant benefits in these patients. Omran *et al*. found in a double-blind, placebo controlled study that daily supplementation of D-ribose for three weeks in 15 NYHA class II-III, CHF patients produced an improvement in diastolic dysfunction parameters ($p<0.02$, $p<0.002$), quality of life ($p\leq0.01$), and physical function scores ($p=0.02$). A reduction in left atrial dimensions, as well as enhancement in left atrial velocity time interval and a shortened E wave deceleration time were observed, signifying improved left ventricular relaxation with an improvement in ventricular compliance, unlike the findings with placebo, in which there were no significant echocardiographic changes or in quality of life parameters [29].

Clinically, CHF patients complain of shortness of breath, persistent fatigue and with progression of their disease, a decrease in ventilatory efficiency. Ventilatory efficiency has been found to be the post powerful predictor of survival in CHF patients. Carter *et al.* reported on 14, NYHA class II-III heart failure, patients with left ventricular dysfunction that supplemental D-ribose for 8 weeks significantly maintained VO_{2max} ($p = 0.02$) and improved ventilatory efficiency ($p = 0.08$) at both the anaerobic threshold and the respiratory compensation point ($p = 0.03$) during sub-maximal exercise [30]. Vijay *et al*. and MacCarter *et al*. have also observed similar improvements in ventilatory efficiency ($p < 0.005$) with an eight week supplementation of D-ribose in separate small cohort studies assessing class III-IV CHF patients. Furthermore, these researchers observed a subjective improvement in quality of life [31, 32]. Since these publications, the awareness and use of D-ribose in CHF patients continues to grow.

D-ribose, important in the PPP, has demonstrated its effective potential in regenerating deficient levels of ATP and increasing the cellular adenine nucleotide pool. The PPP also generates levels of NADPH, important in reducing reactions. The recovery of cellular ATP molecules is important for the maintenance of intracellular processes, to maintain or improve cellular function during times of stress, and potentially lessen any degree of oxidative stress. In a pilot study, Seifert *et al.* reported on seven volunteers in a double, blind cross-over study, who were subjected to a hypoxic state during strenuous exercise. Pre- and post supplementation of D-ribose lessened the production of oxygen free radicals as compared to control. D-ribose lowered urinary malondialdehyde levels while also modifying plasma glutathione status ($p < 0.05$). "Ischemia, hypoxia, intense exercise, and malondialdehyde production are known to reduce glucose 6 phosphate dehydrogenase activity. And, with limited glucose 6 phosphate dehydrogenase activity, NADPH production is suppressed with decreasing concentrations of reduced glutathione, all potentially contributing to a potential elevation in oxygen free radicals" [33].

INTELLECTUAL PROPERTY

Intellectual property has been secured for the uses of D-ribose in enhancing cellular energy levels and also for its use as a metabolic supplement in cardiovascular diseases, such as ischemia and CHF. Sales of nutraceuticals continue to increase either as a novel therapeutic approach or as an

adjunctive measure. Pharmaceuticals can cause undesirable side effects, which can worsen with escalating dosages due to unresponsiveness or progression of disease. Because of these side effects, many patients turn to a more natural approach, i.e. nutraceuticals, such as D-ribose.

The issued "Composition for increasing energy *in vivo*" patent centers on the use of ATP precursors to increase intracellular ATP levels [34]. Pentose carbohydrate supplements can act as a daily dietary additive or as a nutraceutical agent for the regeneration of energy levels in stressful conditions, such as strenuous physical exercise, illness or trauma. Additional agents, such as other metabolites, nutraceuticals, vitamins, minerals, vasodilators, electrolytes, and other balanced dietary substances can be added to any daily dose regimen. As a pentose carbohydrate, D-ribose has demonstrated its potential for regenerating deficient ATP levels following stress via the innate PPP. Again, the ultimate repletion of ATP levels depends on the precursor PRPP. D-ribose is phosphorylated and subsequently produces PRPP levels. As such, D-ribose bypasses the known rate limiting enzymatic steps (glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrongenase) in the PPP, stimulating purine nucleotide metabolism, leading to enhanced ATP synthesis [9, 14]. Supplemental D-ribose enters the PPP beyond these rate limiting steps and thereby stimulates myocardial adenine nucleotide biosynthesis more quickly, enhancing ATP production and replenishing the adenine nucleotide pool [14].

A subsequent issued patent, "Compositions and methods for improving cardiovascular function", further delineates the important significance of D-ribose in patients with cardiovascular diseases [35]. Many patients with cardiovascular diseases have pursued supplemental nutraceuticals, such as D-ribose, coupled with their current pharmaceuticals. This supportive patent centers on methods of supplementing D-ribose alone or in combination with vasodilator agents for improving cardiovascular function for patients afflicted with cardiovascular diseases, including CHF for both acute crises and long term care. Besides the biochemical recovery of ATP, these patients have also experienced an improvement in their quality of life measures and daily activities, potentially reflecting an improvement in their cardiovascular status.

Furthermore, the use of D-ribose peri-operatively has demonstrated both objective and subjective benefits. The administration of D-ribose prior to and post general anesthesia appears to shorten the time to recovery from the known effects of general anesthesia, including cardiovascular and neural consequences. To minimize these potential effects, oral D-ribose was given pre-operatively for elective procedures with an intravenous route of administration during the anesthetic or surgical procedure. Once gastrointestinal function resumes post anesthesia, oral supplementation of D-ribose was continued to sustain the benefit. For emergent procedures, intravenous supplementation of D-ribose provides peri-operative benefits, most pronounced in measured physiological parameters for patients undergoing a variety of surgical conditions. To minimize any state of potential hypoglycemia, co-administration of supplemental dextrose aids in reversing this potential condition [36].

SUMMARY

Myocardial ischemia lowers cellular energy levels, which affects cellular integrity, intracellular processes and function. D-ribose, a natural occurring pentose carbohydrate, is important as a key component of the ATP molecule, in our "genetic material", and has further demonstrated its importance in enhancing deficient cellular energy levels following ischemia. Both pre-clinical animal and subsequent clinical studies have shown that D-ribose can regenerate energy levels, important for intracellular processes and function. Clinically, supplementation with D-ribose has benefited patients afflicted with ischemic cardiovascular diseases, including CHF. D-ribose provides a metabolic/energy link in addressing this cellular energy metabolic deficiency in ischemic heart disease, which has yet to be properly addressed by any current pharmaceuticals. The future of novel efficacious therapies in ischemic heart disease and CHF should address this energy deficient state to achieve maximal therapeutic benefits. An essential need for adequate myocardial energy levels to preserve or maintain cardiac function was proposed by Baliga and Young in a recent publication [8]. They emphasized the relationship between a metabolic deficiency and resultant diastolic dysfunction, in stating that "modulating myocardial energetics could emerge as an important strategy to improve outcomes in diastolic heart failure; the future could very well be in "'revving-up' diastole" [8]. Published results have revealed that D-ribose could play a significant role and should have a meaningful consideration as an additive agent in the therapeutic armamentarium for patients with ischemic cardiovascular disease, including CHF. It is important to address the underlying cellular energy abnormality in ischemic heart disease; and therefore, coupled with current pharmaceuticals could further advance therapies in treating patients afflicted with these diseases.

CURRENT & FUTURE DEVELOPMENTS

The biochemical role that ribose theoretically could play in cellular metabolism is obvious; however, the optimal route of administration continues to be explored. The important need for ribose in future therapies remains to be determined in cardiovascular medicine. Various studies have argued for preserving cellular energy levels, most important in ischemic disease states. Furthermore, studies have reported the relationship between cellular bioenergetics and function, for which future therapeutic approaches and treat-ment regimens must address for more effective outcomes [10, 23].

Past and current investigations have focused on this energy deficient premise to develop strategic advances in correcting this metabolic abnormality. Numerous metabolites and their derivatives have been studied to establish their potential in correcting this cellular energy deficiency. The evaluation of ribose has repeatedly demonstrated its beneficial role in the recovery of this deficient cellular energy state following ischemia, as well as a found improvement in functional parameters. The present knowledge of this natural pentose carbohydrate in the recovery of cellular energy levels in states of stress needs to be further expanded to establish its full potential.

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CONFLICT OF INTEREST

There is no conflict of interest with Dr. Shecterle. Dr. St. Cyr was a past consultant of Bioenergy, Inc. and holds stock options/warrants with Bioenergy, Inc. There was no solicitation by Bioenergy, Inc. in the preparation and production of this article. Ms. Terry holds stock and stock options with Bioenergy, Inc.

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