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D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study

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Abstract

Patients with chronic coronary heart disease often suffer from congestive heart failure (CHF) despite multiple drug therapies. D-Ribose has been shown in animal models to improve cardiac energy metabolism and function following ischaemia. This was a prospective, double blind, randomized, crossover design study, to assess the effect of oral D-ribose supplementation on cardiac hemodynamics and quality of life in 15 patients with chronic coronary artery disease and CHF. The study consisted of two treatment periods of 3 weeks, during which either oral D-ribose or placebo was administered followed by a 1-week wash out period, and then administration of the other supplement. Assessment of myocardial functional parameters by echocardiography, quality of life using the SF-36 questionnaire and functional capacity using cycle ergometer testing was performed. The administration of D-ribose resulted in an enhancement of atrial contribution to left ventricular filling (40 ± 11 vs. 45 ± 9%, $P=0.02$), a smaller left atrial dimension (54 ± 20 vs. 47 ± 18 ml, $P=0.02$) and a shortened E wave deceleration (235 ± 64 vs. 196 ± 42, $P=0.002$) by echocardiography. Further, D-ribose also demonstrated a significant improvement of the patient's quality of life (417 ± 118 vs. 467 ± 128, $P\leqslant0.01$). In comparison, placebo did not result in any significant echocardiographic changes or in quality of life. This feasibility study in patients with coronary artery disease in CHF revealed the beneficial effects of D-ribose by improving diastolic functional parameters and enhancing quality of life.

Keywords: Coronary artery disease; Heart failure; Ribose; Quality of life

1. Introduction

Patients with chronic coronary artery disease often suffer from symptoms of congestive heart failure (CHF), despite multiple drug therapies and repeated cardiac interventions [1]. In addition, quality of life is often lessened in these patients [2]. Previous studies analyzing the effect of ischaemia on myocardial metabolism have reported that a reduction in myocardial adenosine triphosphate (ATP) levels and an accompanying suppression of diastolic function occur following ischaemia [3]. Furthermore, investigations have postulated that an insufficient supply of ATP may play a role in ischaemic CHF [4,5]. Ribose, a naturally occurring pentose sugar, has been shown experimentally to enhance the recovery of depressed myocardial ATP levels and provide improvement in myocardial diastolic compliance following ischaemia [6,7].

Many CHF patients have diastolic dysfunction, and since exogenous supplementation of D-ribose has demonstrated a beneficial effect on diastolic compliance following ischaemia in animal studies, we hypothesized that exogenous supplementation of D-ribose may improve diastolic function and quality of life in patients with CHF. Therefore, this prospective, randomized, double blind, crossover design study was undertaken to assess the effect of oral D-ribose on myocardial function and quality of life in patients with chronic coronary artery disease and CHF.

2. Methods

2.1. Study patients

This prospective, randomized, double blind, crossover design study was conducted at the University of Bonn,

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Bonn, Germany, between July and December 2000. Randomization was balanced between both study groups at the conclusion of the trial. This investigation conformed to the principles outlined in the Declaration of Helsinki. Adult patients with known chronic coronary artery disease with stable angina and heart failure NYHA class II and III were included in this study. Exclusion criteria were <18 years of age, severe concurrent disease (renal failure, diabetes mellitus and neoplasia), evidence of hyperthyroidism and/or the inability to follow the protocol. The study consisted of two treatment periods, each 3 weeks in duration. Initially, by randomization, either oral D-ribose or placebo (dextrose) was administered for 3 weeks. After a wash out period of 1 week, the alternative treatment was administered (crossover arm) for the second 3-week treatment period. Both D-ribose and dextrose are readily metabolized; however, an extended wash out period was provided to ensure that neither test substance would have a carry-over effect into the next arm. Both supplements were supplied as a dry powder, 5 g/dose, dissolved in 8 oz of water, and administered three times a day with meals. D-Ribose and dextrose were not administered according to body mass units; the dose of 5 g was chosen to satisfy both theoretical and financial considerations.

Measured objective parameters of myocardial cardiac function were assessed by transthoracic echocardiography. Subjectively, quality of life using the SF-36 form and functional capacity (exercise tolerance) were also assessed. All parameters were evaluated in patients in both arms of the study, pre- and post-treatment with either D-ribose or placebo. Written informed consent was obtained from all patients and the Institutional Review Board at the University of Bonn, Bonn, Germany, approved the study.

2.2. Echocardiographic studies

The same clinician performed each echocardiographic assessment and two cardiologists analyzed accumulated data in a blinded manner as previously reported [8], with a consensus establishing a final result. All measurements were performed with commercially available equipment (System Vingmed, GE, Norway). To allow off-line quantitative analysis of the echocardiographic data, studies were recorded on videotape with selected cine-loops and velocity spectra digitally transferred to a Macintosh G4 computer (Apple, USA) for subsequent analysis. ECHOPAC® software (GE, Norway) was used for data evaluation.

Each echocardiographic assessment was performed transthoracically and a 1.7/3.4-MHz harmonic transducer was used, with the patient examined in the left lateral decubitus position. A one-lead electrocardiogram was recorded continuously. The 2D mode left atrial dimension was measured at end-systole in the parasternal long-axis view and left ventricular ejection fraction (EF) was determined according to the recommendations of the North American Society of Echocardiography [9]. In addition, left atrial volume was determined using Simpson's rule in the four-chamber view. Transmitral doppler inflow velocities were recorded from the apical four-chamber view with a sample volume positioned between the tips of the mitral leaflets during quiet respiration. The parameters derived from the transmitral velocity spectra were peak velocity of the early (E) and atrial filling (A) waves, the corresponding velocity time integrals (VTI_E and VTI_A) and the percentage of atrial contribution to the total left ventricular filling. The percentage of atrial contribution to the total left ventricular filling was determined by dividing the VTI_A by the total diastolic velocity time integral [10]. The reliability of the echocardiographic measurements was previously reported by our group [11]. In addition, the deceleration slope of the E wave was measured. The results of five consecutive heart cycles were averaged in each patient to obtain a justified value.

2.3. Quality of life and physical function performance

Quality of life in each patient was assessed in a blinded manner by the investigator using the SF-36 questionnaire [12]. These questionnaires were performed at baseline and on completion of each treatment period. All questionnaires were collected by the principal investigator and scored in a blinded manner, according to the SF-36 code. Functional capacity was assessed using a semi-upright exercise ergometer (Siemens, Germany) with incremental increases in the workload to reach a peak-attained watts or maximal exercise work level, characterized by patient fatigue. All tests involved symptom-limited peak exercise performance with at least an exercise-induced peak-attained heart rate of 80–85% of age-predicted peak heart rate. Upper extremity blood pressures were obtained every 2 min and also at peak exercise.

2.4. Statistical analysis

Analysis of variance for repeated measures (ANOVA) was used for the analysis of serial changes of continuous parameters. Further comparisons were subject to a Bonferroni correction. In all cases, a 'P' value $\leqslant 0.05$ was considered statistically significant.

3. Results

Fifteen adult patients were included in the study (14 males/1 female, mean age 61 ± 6 years). Table 1 summarizes the physical characteristics and inclusion criteria of the patients. Coronary artery disease involved two vessels in four patients, and three vessels in the remain-

Table 1
Physical characteristics and inclusion criteria, ($n=15$)

Age (years) (mean ± S.D.)	61 ± 6
Gender	14 males/1 female
Previous MI	
Single	8/15
Multiple	5/15
Left ventricular EF (%)	
Range	28–71
Mean	47.5 ± 1
Coronary artery disease	
Two vessel	4/15
Three vessel	11/15
New York Heart Association (*NYHA*)	
Class II	47%
Class III	53%
Previous intervention (CABG, angioplasty)	5/15

Table 2
Echocardiographic data, ($n=15$)

	Dextrose		Ribose	
	Pre	Post	Pre	Post
LV_d (cm)	132 ± 32	126 ± 23	129 ± 24	128 ± 37
LV_s (cm)	72 ± 29	69 ± 21	64 ± 22	61 ± 28
EF (%)	46 ± 12	45 ± 14	49 ± 11	50 ± 10
Dec rate (ms)	233 ± 70	235 ± 69	235 ± 64	196 ± 42
SV (ml)	60 ± 15	56 ± 16	65 ± 15	67 ± 19
AVTI (ms)	10.2 ± 3.3	10 ± 3.7	7.6 ± 1.9	9.7 ± 2.8#
Atrial con (%)	45 ± 11	44 ± 10	40 ± 11	45 ± 9*
LA Vol (ml)	53 ± 15	55 ± 18	54 ± 20	47 ± 18*

LV_d—left ventricle, end diastole; LV_s—left ventricle, end systole; EF—ejection fraction; dec rate—E wave deceleration time; SV—stroke volume; AVTI—atrial velocity time interval; atrial con—atrial contribution; LA vol—left atrial volume; *$P<0.02$ pre vs. post, #$P<0.002$ pre vs. post.

ing patients. Forty-seven percent ($n=7$) of the patients were in NYHA class II, with the remaining in class III ($n=8$) at the time of entry into the study. EF in this cohort ranged between 28 and 71%, with a mean EF of 47.5 ± 1%. All except two patients had a previous history of myocardial infarction, with five patients having two or more previous infarcts. Five patients had previously undergone either coronary artery bypass or coronary angioplasty. All patients were on nitrates, molsidomin and β-blockers. Three patients were also on diltiazem and an additional three patients were on trapidil. Medications were not altered during the study. Seven patients were treated with D-ribose first and then changed to dextrose. The remaining eight patients started with dextrose before changing to ribose. All patients were compliant throughout the study and completed both treatment periods. Each patient underwent both subjective and objective assessment.

3.1. Echocardiography

Echocardiographic data pre- and post-treatment with either D-ribose or placebo is presented in Table 2. Neither D-ribose nor placebo significantly affected left ventricular volume, stroke volume or left ventricular EF. On the other hand, analysis of diastolic function parameters revealed significant findings. D-Ribose resulted in a significantly shorter deceleration time of the E wave, with a significantly smaller left atrial volume and a higher percentage of atrial contribution to left ventricular filling as compared to patients treated with placebo.

3.2. Functional capacity and quality of life

Table 3 represents the analyzed data for functional capacity and quality of life for the treated groups. All patients completed exercise testing with no adverse effects. During testing, the peak work capacity was not changed by either treatment. However, there was a difference in effect on quality of life, evaluated by the SF-36 questionnaire, observed between the groups (Table 3). Patients receiving oral D-ribose demonstrated a significant improvement in the overall score of the quality of life index from 417 ± 118 to 467 ± 128 ($P \leqslant 0.01$). Furthermore, this increase was paralleled by a significant change in physical function from 48 ± 23 to 54 ± 21 ($P=0.02$). These parameters did not change significantly with placebo (quality of life index 420 ± 144 vs. 463 ± 160 ($P=0.73$), and physical function 52 ± 20 vs. 56 ± 24 ($P=0.21$)).

Table 3
Quality of life, physical function, functional capacity data, ($n=15$)

	Dextrose		Ribose	
	Pre	Post	Pre	Post
Quality of life	420 ± 144	463 ± 160	417 ± 118	467 ± 128*
Physical function	52 ± 20	56 ± 24	48 ± 23	54 ± 21**
Funct cap (peak-attained watts)	102 ± 19	100 ± 10	100 ± 18	103 ± 15

Funct cap—functional capacity.
* $P<0.01$.
** $P<0.02$.

4. Discussion

ATP is essential to all cells to maintain their integrity and function. Normally, the demand and supply of ATP molecules is maintained; however, during and following states of ischaemia or hypoxia, tissue energy levels can become depressed, where supply does not meet demand. Animal studies have confirmed that acute and chronic ischaemia leads to impaired cardiac energy metabolism, in particular ATP deficiency, and a considerable amount of time is required for these levels to return to normal. This period of suppressed energy levels is reflected in a temporal state of diastolic dysfunction [4,7].

Several studies have shown that the pentose sugar, D-ribose, shortens the time to regenerate deficient myocardial ATP levels following ischaemia [13,14]. D-Ribose aids cardiac metabolism by entering the pentose phosphate pathway to form ribose-5-phosphate and bypasses the rate-limiting enzymes of glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase [4]. Decreased availability of myocardial ATP may allow calcium to remain fixed to troponin longer in diastole, leading to diastolic dysfunction, as previously reported in animal studies [4].

Clinically, exogenous ribose has been reported to provide a benefit to patient's with stable coronary artery disease [15]. Patients receiving 15 g of D-ribose, four times per day, demonstrated their ability to better tolerate exercise-induced ischaemia. During treadmill exercise, ribose supplementation allowed patients to exercise for a significantly longer time before developing ST changes or the occurrence of moderate angina [15]. Our study is the first clinical report to demonstrate that oral supplementation with D-ribose enhances diastolic function in humans with coronary artery disease and CHF. D-Ribose substantially improved atrial contribution to left ventricular filling in our patient cohort. This improvement in atrial contribution to left ventricular filling was paralleled by a normalization of the deceleration slope of the E wave of the mitral inflow pattern and by a decrease in the volume of the left atrium. These effects were not observed with placebo treatment. The improvements in diastolic parameters reflect a more efficient relaxation phase of the heart, an entity commonly deficient and of therapeutic importance in patients with chronic coronary artery disease and CHF. However, a significant improvement in systolic function with D-ribose supplementation, as assessed by left ventricular functional parameters with D-ribose supplementation, was not found. Pauly and Pepine reported that 'complete restoration of ATP levels actually lags behind normalization of many indices of systolic cardiac function' [4]. However, it is also possible that the predominant effect of D-ribose centers on the relaxation phase of the heart and over time the remodeling or conditioning of this aspect of cardiac function could positively support a change in systole. Furthermore, it is possible that D-ribose may cause changes in systolic function during exercise; however, echocardiographic evaluation was not performed at the end of exercise.

This study also demonstrated that D-ribose improved the patient's quality of life. Furthermore, the improvement in quality of life was paralleled by an increase in physical function, reflecting exercise tolerance. Nevertheless, we did not find a difference in peak-attained watts or maximal exercise work, as assessed by work rate pre- and post therapy with D-ribose. This was not surprising because peak exercise levels have been shown to poorly correlate with systolic function, assessed by EF, in patients with CHF [16]. The finding of an improvement in the subjective assessment in physical function may be explained by the enhancement in diastolic function in these patients receiving D-ribose. Further, diastolic function has been reported to correlate well with patient functional capacity as reported by Sumimoto et al. [17]. They found that in patients with left ventricular systolic dysfunction following myocardial infarction, the major cause of exercise impairment and failure to increase left ventricular performance during exercise is associated with diastolic dysfunction with the presence of non-infarct-related coronary lesions that have the potential for exercise-induced ischaemia [17].

4.1. Clinical implications

The finding of an improved quality of life assessment and diastolic functional parameters in chronic coronary artery disease and CHF patients when receiving D-ribose supplementation may offer an alternative treatment for these patients or an accompaniment to patients that have failed standard therapeutic regimens.

4.2. Limitations

The cohort of this feasibility study was small, only 15 patients. However, the study was designed and conducted in a prospective, randomized, double blind, crossover design format. Furthermore, exact assessment of diastolic function by echocardiography has its own limitations. In addition, echocardiographic measurements were only evaluated at rest, although stress testing was used to determine if there was a difference in peak watts attained during exercise. Gas exchange parameters may aid in describing a more detailed interpretation on submaximal indices, such as ventilatory efficiency slope or a linear relationship between minute ventilation and expired carbon dioxide ($\dot{V}E/\dot{V}CO_2$). This question has to be evaluated by further studies.

References

[1] Topol EJ, Serruys PW. Frontiers in interventional cardiology. Circulation 1998;98:1802–20.

[2] Task Force of the European Society of Cardiology. Management of stable coronary angina pectoris. Eur Heart J 1997; 18:394–413.
[3] Reibel DK, Rovetto MJ. Myocardial ATP synthesis and mechanical function following oxygen deficiency. Am J Physiol 1978;234:H620–H626.
[4] Pauly DF, Pepine CJ. D-Ribose as a supplement for cardiac energy metabolism. J Cardiovasc Pharmacol Therapeut 2000;5(4):249–58.
[5] Dzeja PP, Redfield MM, Burnett JC, Terzic A. Failing energetics in failing hearts. Curr Cardiol Rep 2000;2(3):212–7.
[6] Sole MJ, Jeejeebhoy KN. Conditional nutritional requirements and the pathogenesis and treatment of myocardial failure. Curr Opin Clin Nutr Metab Care 2000;3(6):417–24.
[7] Tveter KJ, St. Cyr JA, Bianco RW, Einzig S, Foker JE. Ribose enhanced recovery of diastolic function after global myocardial ischemia. Ped Res 1988;23:226A (abstract).
[8] Omran H, Jung W, Rabahieh R, et al. Left atrial chamber and appendage function after internal atrial defibrillation: a prospective and serial transesophageal echocardiographic study. J Am Coll Cardiol 1977;29:131–8.
[9] Henry WL. Report of the American Society of Echocardiography Committee on nomenclature and standards in two-dimensional echocardiography. Circulation 1980;62:212–7.
[10] Manning WJ, Leeman DE, Gotch PJ, Come PC. Pulsed doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. J Am Coll Cardiol 1989;13:617–23.
[11] de Divitiis M, Omran H, Rabahieh R, et al. Right atrial appendage thrombosis in atrial fibrillation: its frequency and its clinical predictors. Am J Cardiol 1999;84:1023–8.
[12] Ware JE Jr.. John E. Ware Jr. on health status and quality of life assessment and the next generation of outcomes measurement. Interview by Marcia Stevic and Katie Berry. J Healthc Qual 1999;21(5):12–7.
[13] St. Cyr JA, Bianco RW, Schneider JR, et al. Enhanced high energy phosphate recovery with ribose infusion after global myocardial ischemia in a canine model. J Surg Res 1989;46:157–62.
[14] Zimmer HG. Normalization of depressed heart function in rats by ribose. Science 1983;220:81–2.
[15] Pliml W, Von Arnim T, Stablein A, Hofmann H, Zimmer HG, Erdmann E. Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. Lancet 1992;340:507–10.
[16] Cohn JN. Overview of the treatment of heart failure. Am J Cardiol 1997;80(11A):2L–6L.
[17] Sumimoto T, Jikuhara T, Hattori T, et al. Importance of left ventricular diastolic function on maintenance of exercise capacity in patients with systolic dysfunction after anterior myocardial infarction. Am Heart J 1997;133:87–93.