Ther Adv Cardiovasc Dis
2015, Vol. 9(3) 56–65
DOI: 10.1177/1753944715572752



# D-Ribose aids heart failure patients with preserved ejection fraction and diastolic dysfunction: a pilot study

**Melike Bayram, J.A. St. Cyr and William T. Abraham**

***Abstract***

**Objectives:** The incidence of heart failure continues to escalate with >550,000 newly diagnosed patients annually worldwide. More than half of the patients with heart failure have preserved ejection fraction or isolated diastolic dysfunction, for which no current effective therapies for diastolic dysfunction exist. Every cell requires adequate levels of high energy phosphates to maintain integrity and function. Previous studies have demonstrated that diastolic function is energy dependent and supplemental D-ribose has shown to improve diastolic dysfunction. This study investigated what role D-ribose might play in congestive heart failure patients with preserved systolic function and diastolic dysfunction.

**Methods:** A total of 11 patients, New York Heart Association class II–IV, with clinical symptoms, normal left ventricular systolic function and echocardiographic evidence of diastolic dysfunction were enrolled after meeting inclusion criteria. Each patient received oral D-ribose (5 g/dose) for 6 weeks. Echocardiographic evaluation, cardiopulmonary metabolic testing and subjective questionnaire assessment were performed at baseline, 6 weeks and at 9 weeks (3 weeks after discontinuing D-ribose).

**Results:** An improvement in their tissue Doppler velocity (E′), which was maintained at 9 weeks, was demonstrated in 64% of the patients. Five patients showed an improvement in their ratio of early diastolic filling velocity (E) to early annulus relaxation velocity (E′). There was no appreciable difference in these measurements during valsalva or with leg raising and handgrip exercises. Four patients also had an improvement in their maximum predicted $VO_2$ values; two demonstrated a worsening effect and no differences were noted in the remaining patients. Subjective assessment revealed a benefit in only one patient, worsening symptoms in one patient and no change in the remaining cohort.

**Conclusions:** This pilot study revealed some beneficial trends with D-ribose even with this small cohort size. However, future investigations are necessary to further substantiate these observed benefits.

***Keywords:*** diastolic dysfunction, D-ribose, heart failure, preserved systolic function

## Introduction

Cardiovascular disease is the leading cause of death worldwide and the incidence of heart failure continues to escalate with >550,000 newly diagnosed patients annually. More than half of patients with heart failure have preserved ejection fractions or isolated diastolic dysfunction [Bursi *et al.* 2006]. Current therapeutic approaches and ongoing research have focused on improving diastolic and/or systolic dysfunction; however, current therapies, including both device-related and pharmaceuticals, to improve diastolic dysfunction have not been successful [Zile and Brutsaert, 2002]. Investigations continue to discover potential therapy at improving diastolic dysfunction, including a metabolic approach.

Every cell requires adequate amounts of energy to maintain its integrity and function. Various studies have reported that a deficiency in high energy

Correspondence to:
**J. A. St. Cyr, MD, PhD**
Jacqmar, Inc., 10965 53rd Ave. No., Plymouth, MN 55442, USA
**congenital@aol.com**

**Melike Bayram, MD**
**William T. Abraham, MD**
Cardiovascular Medicine, Ohio State University, Columbus, OH, USA

phosphates, i.e. adenosine triphosphate (ATP), occurs in ischemic heart disease, including ischemic heart failure [Ibel and Zimmer, 1986; Ingwall and Weiss, 2004; St Cyr *et al.* 1989]. Schneider and colleagues demonstrated that a temporal correlation exists between myocardial ATP levels and diastolic function following a myocardial ischemic insult [Schneider *et al.* 1985]. Supplementation with D-ribose (DR) during and following this ischemic insult produced a rapid return in ATP levels, as well as an improvement in diastolic dysfunction due to the ischemia.

Numerous studies have further reported the benefit of DR, a natural occurring pentose carbohydrate, in replenishing deficient ATP levels following a cellular insult, including myocardial ischemia. DR is involved in an important pathway that bypasses a key metabolic enzyme needed for the production of ATP during ischemic conditions. Myocardial ischemia is an underlying etiology in many congestive heart failure patients. Further, Ingwall and Weiss reported that the failing heart is energy starved; therefore, efforts to increase myocardial energy levels in an energy compromised myocardium may show promise [Ingwall and Weiss, 2004].

Due to the metabolic benefit of DR during and following myocardial ischemia, we investigated in this pilot study the potential role of DR as a therapeutic agent to improve diastolic function in patients with congestive heart failure, presenting with preserved systolic function and diastolic dysfunction.

## Methods

This pilot study was approved by the institutional committee on human research at the Ohio State University. The study and the procedures used in this study followed in accordance with the ethical standards of the responsible committee on human experimentation (Institutional or regional) or with the Declaration of Helsinki 1975, revised Hong Kong 1989.

Heart failure patients were screened from the outpatient heart failure and cardiology clinics at Ohio State University, Columbus, OH. A total of 11 adult patients with New York Heart Association (NYHA) class II–IV clinical symptomatology, normal left ventricular (LV) systolic function and echocardiographic evidence of diastolic dysfunction were found eligible for this study, based on the inclusion and exclusion criteria (Table 1). Informed consent was obtained from all patients following enrollment. Each patient consumed oral DR [5 g, three times a day (TID)] for 6 weeks. Each 5 g/dose of DR was added to their chosen beverage during a meal or the DR was added directly to their meal itself. All patients underwent a baseline echocardiogram, assessing diastolic parameters, and cardiopulmonary metabolic testing. These objective study endpoints were repeated at 6 weeks and at 9 weeks (3 weeks after discontinuing DR). Subjectively, the patient completed the Minnesota Living with Heart Failure Questionnaires (MLWHFQ) at each of the above time points.

The endpoint assessments of this study included resting echocardiographic, diastolic functional parameters, ventilation treadmill exercise evaluation, as well as subjective questionnaires. Echocardiographic assessment of diastolic dysfunction involved standard methods of Doppler echocardiography, performed at rest. The following diastolic functional indices were evaluated: rate of mitral inflow deceleration time of the E wave; ratio of early diastolic filling velocity (E) to late diastolic filling velocity (A) (E/A ratio); ratio of mitral filling velocity (E) to early annulus relaxation velocity (E′) (E/E′ ratio); isovolumetric relaxation time (IVRT); left atrial volume and area; LV volume and size; LV ejection fraction (LVEF); assessment of mitral regurgitation and stenosis; and right ventricular systolic pressure when available based on the presence of tricuspid regurgitation. E wave measurements were obtained at both the septal and lateral corner aspects of the mitral annulus using a four-chamber apical view. The E wave deceleration time may not elicit an accurate determination of LV stiffness if LV relaxation is unknown [Shmuylovich and Kovacs, 2007]. Furthermore, studies have reported that the E/E′ ratio maybe a strong predictor of future cardiac events [Acil *et al.* 2005]. The mitral inflow velocities were also measured during a valsalva maneuver, leg raising exercise and hand gripping exercise. Left atrial and ventricular volumes were determined using two-dimensional (2-D) echocardiogram (2-D echo).

Cardiopulmonary metabolic testing was performed using a modified Naughton treadmill protocol, evaluating a patient's ventilation during exercise. Patients were encouraged to perform maximal exercise up to exhaustion. The Borg scale (0–20 levels) was used as a subjective level of assessment

**Table 1.** Study entrance criteria.

| |
|---|
| **INCLUSION:** |
| (1) Confirmed diagnosis of CHF (NYHA classes II–IV) |
| (2) Previously diagnosed with diastolic dysfunction by echocardiography |
| (3) At least 3 months of standard, conventional drug therapy for their treatment of heart failure |
| (4) In sinus rhythm during metabolic exercise testing |
| (5) Left ventricular ejection fraction (LVEF) >45% |
| (6) Ability to participate in treadmill exercise testing |
| (7) Signed written consent |
| **EXCLUSION:** |
| (1) Echocardiographic evidence of ventricular aneurysm with dyskinesis |
| (2) Prior diagnosis or known history of moderate to severe COPD |
| (3) Uncontrolled systolic/diastolic hypertension (patients with SBP > 140 or DBP > 90 will be excluded) |
| (4) Prior diagnosis or known history of type I diabetes |
| (5) Echocardiographic evidence of severe valvular heart disease (more than trivial or mild or moderate valvular stenosis or regurgitation on surface echocardiogram) |
| (6) Systolic dysfunction with LVEF ⩽ 45% |
| (7) Pregnancy |
| (8) Recent use of D-ribose(within the last 6 months) as a supplement |

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure.

for exhaustion for both fatigue and dyspnea. The following gas exchange variables were assessed: oxygen uptake (ml/min); carbon dioxide ($CO_2$) production (ml/min); minute ventilation (l/min); respiratory exchange ratio (ratio of carbon dioxide output to oxygen uptake); and the minute ventilation to minute $CO_2$ production ratio.

### *Statistical analysis*

Data are presented as mean ± standard error (SE) of the mean. The data were analyzed using a paired *t*-test for dependent variables with alpha level of $p < 0.05$ used for statistical significance.

## Results

All enrolled adult patients (6 females, 5 males), mean of 65 years of age, tolerated the consumption of DR without any adverse effects. All patients presented with NYHA class II–III symptoms (mean 2.4) with a mean LVEF of 60%. A history of coronary arterial revascularization for coronary artery disease without evidence of recurrent myocardial ischemia was recorded for 3 out of 11 patients (Table 2). One patient refused to walk on the treadmill after the baseline study and one patient could not participate in the 9 week follow-up treadmill testing due to an accidental injury unrelated to the study.

After 6 weeks of oral DR therapy, 7 out of 11 patients showed an improvement in their tissue Doppler velocity (E′) (Figure 1), with this improvement maintained at the 9 week follow-up visit. Five patients showed improvement in their E/E′ ratios, which provided a reasonable estimation of LV end diastolic pressure (Figure 2). These measurements were repeated during valsalva, leg raising exercise and hand gripping exercise. However, there were no differences between measured tissue Doppler velocity values or the E/E′ ratios during induced valsalva, as well as during leg raising and hand gripping exercises (Figures 1 and 2). Overall, there was a statistically nonsignificant tendency towards improved diastolic function as measured by septal and lateral E′ values (Figure 3), with a 16% increase in the lateral E′ (Table 3). We did not see any tendency towards improvement or worsening in the other assessed diastolic parameters for deceleration time (Dec T), IVRT, and ventilatory equivalent for carbon dioxide ($VE/VCO_2$), Figures 4 and 5.

In terms of cardiopulmonary metabolic testing, four patients improved their maximum predicted $VO_2$ values, whereas two had mild worsening and no change noted in the remaining patients (Figure 6). Subjective assessments by MLWHFQ at weeks 0, 6 and 9 revealed no statistical significant differences in 9 patients. One patient showed

**Table 2.** Baseline entrance characteristics.

| | Mean ± SE | Range |
|---|---|---|
| Age, years | 65 ± 3.7 | 48–87 |
| LVEF | 59.7 ± 2 | 49–67 |
| NYHA class | 2.36 ± 0.15 | 2–3 |
| LVEDV (ml) | 83.75 ± 6.32 | 53.9–115.9 |
| LVESV (ml) | 34.5 ± 4.17 | 18.28–61.72 |
| LAA ($cm^2$) | 19.9 ± 1.28 | 13.15–25.74 |
| LAESV (ml) | 61.6 ± 5.51 | 33.91–83.57 |
| LAESV Index | 31.83 ± 3.03 | 19.2–55.2 |
| Max. $VO_2$ (ml/kg/min) | 15.3 ± 1.2 | 10.2–21.1 |
| $VE/VCO_2$ | 31.9 ± 1.3 | 25–38 |
| Max. predicted $VO_2$ (%) | 16.8 ± 5.1 | 73–124 |

LAA, left atrial area; LAESV, left atrial end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; Max $VO_2$, maximum rate of oxygen consumption during incremental exercise; NYHA, New York Heart Association; SE, standard error; $VE/VCO_2$, ventilator equivalent for carbon dioxide.

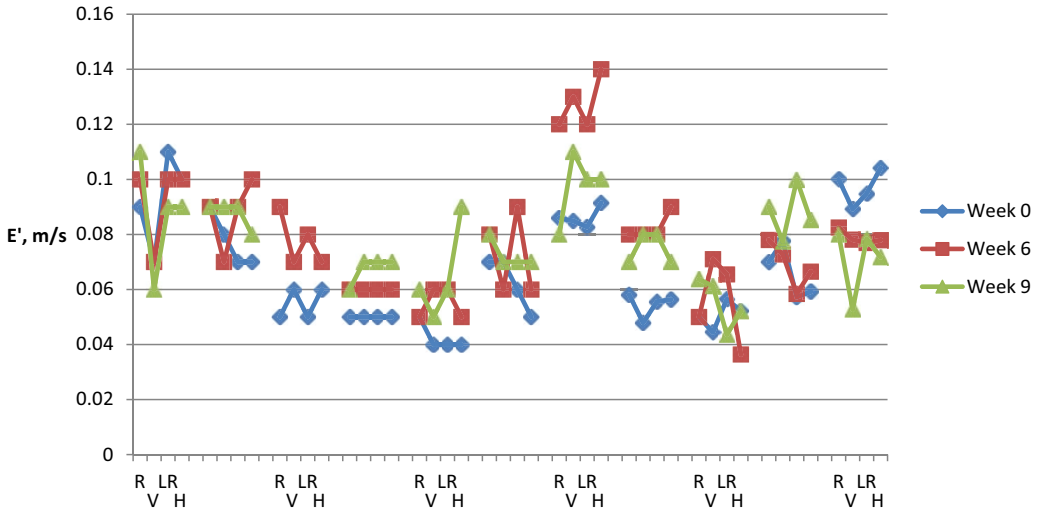


**Figure 1.** E′ lateral values for 11 patients.
E′, early annulus relaxation velocity; H, hand gripping; LR, leg raising; R, rest; V, valsalva.

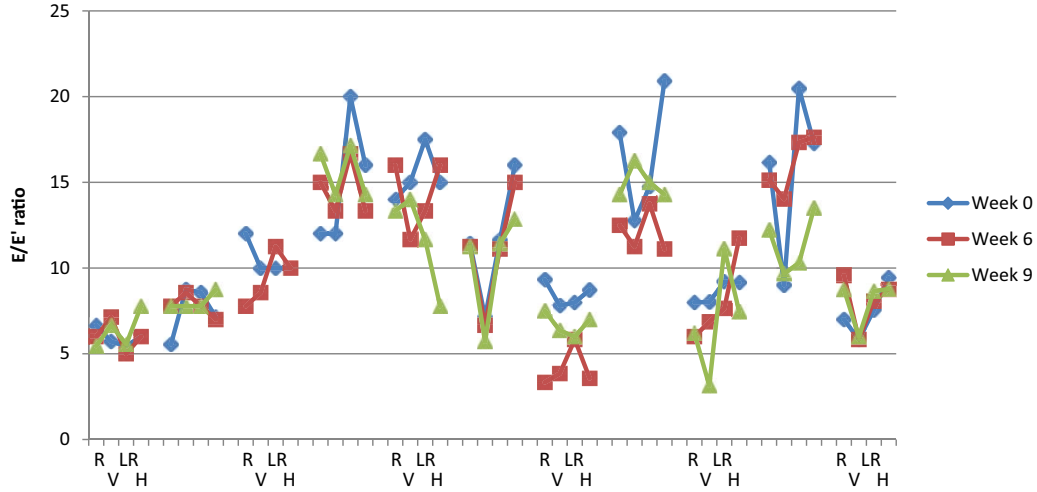


**Figure 2.** E/E′ ratio data for 11 patients.
E, mitral filling velocity; E′, early annulus relaxation velocity; H, hand gripping; LR, leg raising; R, rest; V, valsalva.

**Table 3.** Measured echocardiographic diastolic functional parameters.

| | Week 0 | Week 6 | Week 9 | p1 | p2 |
|---|---|---|---|---|---|
| Lateral E′ (m/s) | | | | | |
| Rest | 0.069 | 0.08 | 0.078 | 0.057 | 0.11 |
| valsalva | 0.065 | 0.075 | 0.072 | 0.12 | 0.31 |
| Septal E′ (m/s) | | | | | |
| Rest | 0.052 | 0.058 | 0.052 | 0.13 | 0.98 |
| valsalva | 0.045 | 0.055 | 0.09 | 0.14 | 0.22 |
| E/E′ ratio | | | | | |
| Rest | 10.8 | 10 | 10.34 | 0.39 | 0.6 |
| valsalva | 9.2 | 8.9 | 8.9 | 0.61 | 0.77 |
| E/A ratio | | | | | |
| Rest | 1.19 | 1.9 | 1.33 | 0.37 | 0.24 |
| valsalva | 0.98 | 1.06 | 1.03 | 0.14 | 0.56 |
| Dec T (ms) | | | | | |
| Rest | 225.8 | 239.5 | 218.2 | 0.44 | 0.67 |
| valsalva | 272.7 | 267.6 | 246.8 | 0.89 | 0.29 |
| IVRT (ms) | | | | | |
| Rest | 84.9 | 95.79 | 90.8 | 0.46 | 0.44 |
| valsalva | 91.7 | 107.7 | 93.7 | 0.21 | 0.76 |
| LAESV index | 31.8 | 34.5 | 33.7 | 0.33 | 0.41 |
| LAA index | 10.3 | 10.7 | 10.5 | 0.49 | 0.69 |
| Max. $VO_2$ (ml/kg/min) | 15.3 | 15.3 | 15.5 | 0.98 | 0.78 |
| $VE/VCO_2$ | 31.9 | 32.9 | 34.9 | 0.31 | 0.03 |
| Max. predicted % $VO_2$ | 99.1 | 100.6 | 108 | 0.71 | 0.66 |
| MLWHFQ score | 42.4 | 42.2 | 37.4 | 0.98 | 0.30 |

A, late diastolic filling velocity; E, early diastolic filling velocity; E′, early annulus relaxation velocity; IVRT, isovolumetric relaxation time; LAA, left atrial area; LAESV, left atrial volume in end systole; Max. $VO_2$, maximum rate of oxygen consumption during incremental exercise; MLWHRQ, Minnesota Living with Heart Failure Questionnaire; Dec T, deceleration time; $VE/VCO_2$, ventilator equivalent for carbon dioxide.

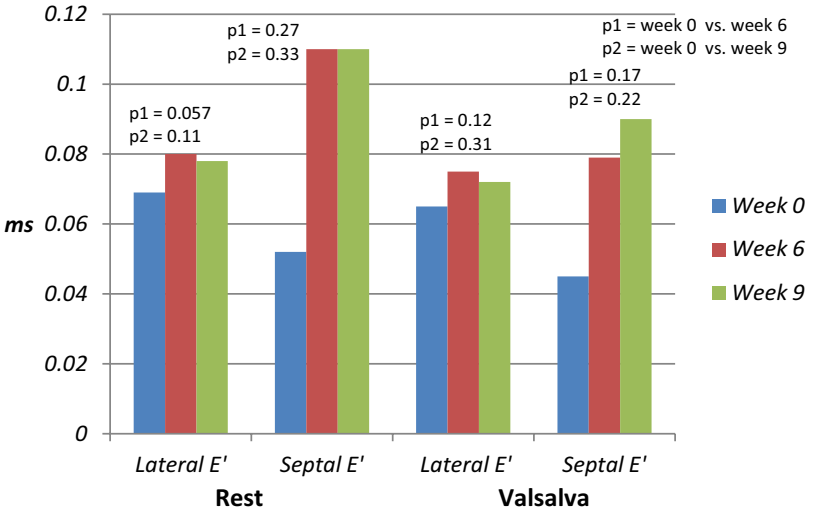


**Figure 3.** Septal and lateral E′ values.
E′, early annulus relaxation velocity.

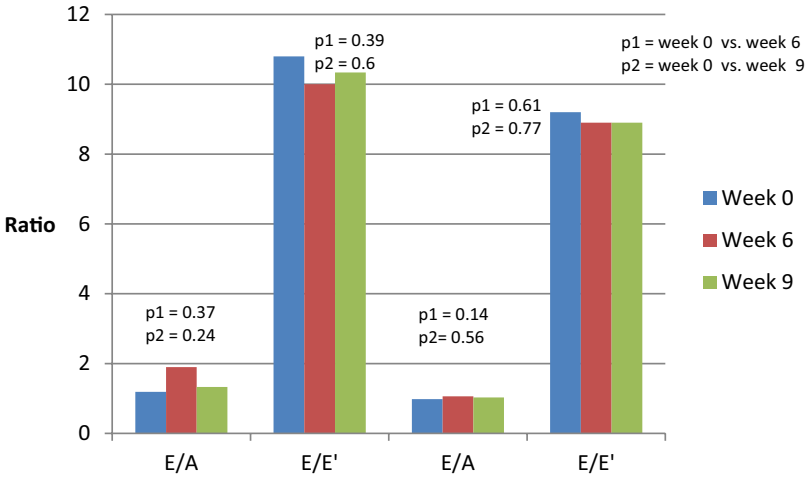


**Figure 4.** E/A and E/E′ ratio values.
A, late diastolic filling velocity; E, early diastolic filling velocity; E′, early annulus relaxation velocity.

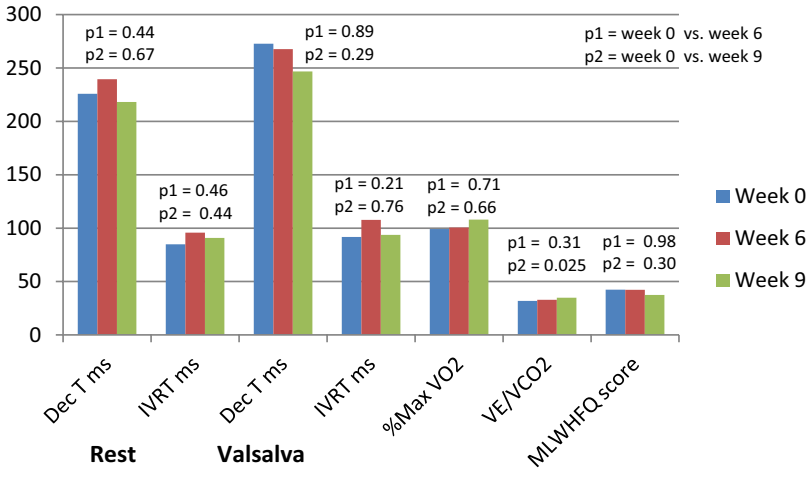


**Figure 5.** Additional cardiopulmonary assessment parameters.
IVRT, isovolumetric relaxation time; Max $VO_2$, maximum predicted $VO_2$; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; $VE/VCO_2$, ventilatory equivalent for carbon dioxide; Dec T, deceleration time.

improvement in symptoms, with worsening of the MLWHFQ score in another patient (Figure 7).

## Discussion

The incidence of heart failure continues to increase worldwide. Many of these affected patients with heart failure have a component of diastolic dysfunction. Currently, there is no approved effective treatment for diastolic dysfunction. Any effective therapy for diastolic heart failure depends on a fundamental understanding of the underlying mechanisms responsible for this dysfunctional state, and thereby direct future therapies targeted at correction of this functional abnormality.

Diastolic dysfunction can develop due to both intrinsic and extrinsic mechanisms. These can include changes in calcium homeostasis caused by: (1) abnormalities in the sarcolemma channels; (2) abnormal sarcoplasmic reticulum calcium (SR $Ca^{2+}$) reuptake caused by a decrease in SR $Ca^{2+}$ ATPase; and (3) changes in the phosphorylation state of the proteins that modify SR $Ca^{2+}$ ATPase function such as phospholamban, calmodulin and calsequestrin. Alterations in any of these processes can result in an increase in the cytosolic calcium concentration, prolongation in the calcium transient, and delay in the diastolic decline in cytosolic calcium concentration. When these alterations in calcium homeostasis occur in cardiac disease, the ability for relaxation is

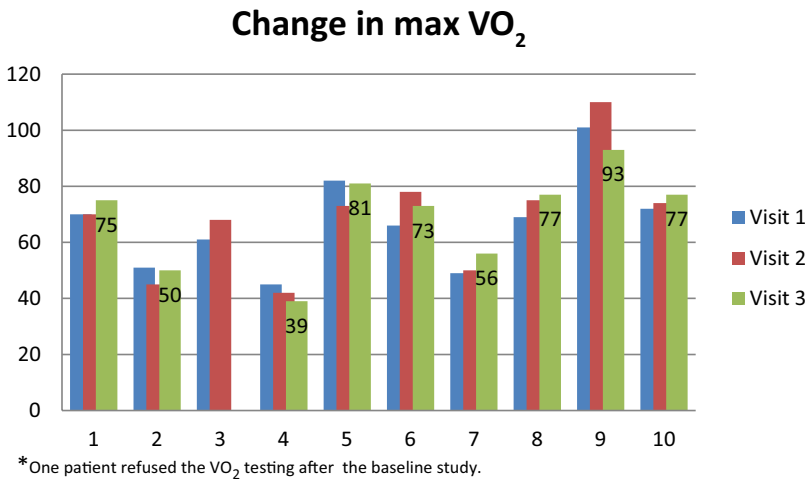


**Figure 6.** Maximum predicted $VO_2$ data.
Max $VO_2$, maximum rate of oxygen consumption during incremental exercise.

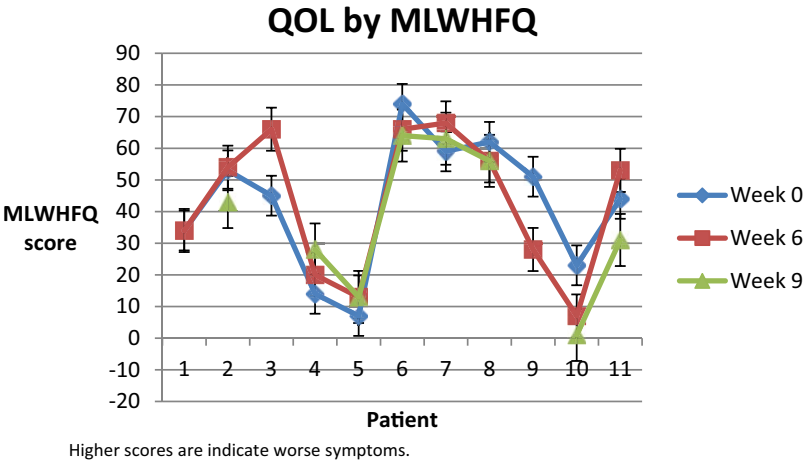


**Figure 7.** Quality of life (QOL) data by Minnesota Living with Heart Failure Questionnaire (MLWHFQ).

affected, as well as a developed state of passive stiffness. During relaxation, ATP hydrolysis is required for myosin to detach from actin, for the calcium dissociation from troponin C (Tn-C) and active sequestration of calcium by the SR. Modification of any of these steps alters diastolic function. Thus, relaxation is an energy-consuming process. To maintain normal myocardial diastolic function, the concentration of the products of ATP hydrolysis [adenosine diphosphate (ADP) and inorganic phosphate (Pi)] must remain low with an appropriate ADP/ATP ratio. Diastolic dysfunction occurs if the absolute concentration of ADP or Pi increases, or if the relative ratio of ADP/ATP rises. An abnormality in this energetic state is caused by a limited ability to recycle ADP to ATP [Zile and Brutsaert, 2002]. Thus, an adequate supply of high energy phosphates is crucial to maintain the cell's integrity and function.

Various preclinical animal studies have consistently reported that a deficiency in myocardial ATP levels occur follows ischemia. This depletion in high energy phosphates following ischemia has been investigated in isolated rat hearts as well as in a chronic canine model [Ibel and Zimmer, 1986; St Cyr *et al.* 1989; Zimmer and Ibel, 1984]. Ward and colleagues reported that there is an approximate 50% reduction in myocardial ATP levels following a moderate 20 min global ischemic insult, for which an extended period of time is required for total recovery [Ward *et al.* 1984]. Furthermore, Kriett and colleagues found a temporal correlation exists between myocardial ATP levels and

diastolic function following global myocardial ischemia. As myocardial ATP levels fell, a state of diastolic dysfunction developed [Kriett *et al.* 1983]. This depletion in high energy phosphates is also present in heart failure. Ingwall and Weiss reported that myocardial energy levels are low with the heart being 'energy starved' in heart failure [Ingwall and Weiss, 2004]. Therefore, therapeutic options should give strong consideration to addressing this energy deficiency, with a metabolic approach in efforts to replenish these depressed myocardial energy levels with restoration of the adenylate energy charge to aid in maintaining or improving myocardial function.

Previous animal studies have shown that the supplementation of DR following a myocardial ischemic insult improves the recovery of ATP levels as well as LV function [St Cyr *et al.* 1989; Tveter *et al.* 1988; Zimmer and Ibel, 1984]. ATP levels can decrease by 40–70% and total adenine nucleotides decrease by 35–50% post 10–30 minutes of ischemia, depending upon the study protocol. Despite reperfusion, these levels remain depressed for 1–7 days. In one study, supplementation with a DR infusion during reperfusion and continued for 24 additional hours following 20 min of global myocardial ischemia improved ATP levels to 85% of baseline, whereas ATP levels did not improve in control dogs not receiving DR [St Cyr *et al.* 1989]. Schneider and colleagues reported that diastolic dysfunction improved as ATP levels recovered in DR treated animals unlike controls [Schneider *et al.* 1985].

Clinically, DR has been investigated in various avenues in cardiovascular medicine. Pliml and colleagues investigated the effects of DR during treadmill exercise in patients with coronary artery disease (CAD) [Pliml *et al.* 1992]. A total of 24 patients with severe and stable CAD were exercised to the point of producing anginal symptoms and ST depression. Those with reproducible times to angina on repeat testing were randomized to 3 day course of oral DR or placebo. Patients were exercised again on day 5; the DR group demonstrated a significant improvement in their time to angina and their time to ST depression [Pliml *et al.* 1992]. In further studies, DR infusion has been shown to enhance the identification of viable, ischemic myocardial segments both by thallium-201 redistribution and dobutamine stress echocardiography. This is likely because DR detects additional areas of hibernating myocardium by promoting 5-phospho-α-D-ribosyl 1-pyrophosphate (PRPP) synthesis and increasing ATP levels necessary for thallium uptake [Hegewald *et al.* 1991; Perlmutter *et al.* 1991; Sawada *et al.* 2009]. Most recently, DR was studied in 143 patients with CAD who underwent revascularization with 'off' pump cardiopulmonary bypass surgery. A total of 66 of these patients had presented with acute myocardial infarction (MI). All patients received peri-operative oral DR supplementation. Cardiac indices (CI) were measured both pre and post operatively and DR produced an increase in CI by 43% postoperatively, compared with only a 13% improvement found with historical controls [Perkowski *et al.* 2007].

There have only been few studies looking at effects of DR on diastolic function. A preclinical animal model (canines) demonstrated an improvement in both adenine nucleotide levels and ventricular compliance with DR, following 20 minutes of global ischemia [Tveter *et al.* 1988]. Clinically, Omran and colleagues reported an improvement in left atrial size and E wave deceleration times, as well as an improvement in quality of life assessment with oral DR in patients with congestive heart failure (LVEF 27–72%) [Omran *et al.* 2003]. These data were encouraging and additional studies are necessary to further support the role of DR as a potential therapeutic agent for maintaining and improving ventricular diastolic function.

Based on the data available from prior studies, we hypothesized that supplemental DR offers a means to improve deficient myocardial energy commonly found in ischemic heart disease, as well as the potential to improve diastolic dysfunction in this population. We chose echocardiography as the tool for assessing diastolic function given its noninvasiveness and easy availability. Our findings were not as encouraging as the findings from prior reported studies. We observed a tendency towards better diastolic function by echocardiographic criteria; however, this was not statistically significant likely secondary to the small sample size. We are also unsure of the clinical significance of the 16% increase in the mean tissue Doppler velocity, as we did not see any improvement in other clinical parameters ($VO_2$ and MLWHFQ). Our study enrolled patients with normal LV systolic function only. Also, few patients in our study had CAD, whereas previously, DR was shown to offer the greatest benefit in patients with ischemic heart disease.

## Limitations

We believe that the absence of strongly positive results from this study are at least partially secondary to the limitations of the study including small sample size, short duration of treatment and short duration of follow up. Also, our assessment of the diastolic function was limited by the usual limitations of echocardiography. We noted that for patients who happened to have both noninvasive and invasive assessment at the time of enrollment, echocardiogram tended to underestimate the severity of the diastolic dysfunction compared with an invasive method. More direct assessment of LV diastolic relaxation and/or stiffness *via* invasive methods may eliminate these limitations and provide more accurate evaluation of the effects of DR on myocardial diastolic function. Further, some of the previous studies that showed significantly positive effects of DR on LV function used intravenous formulated DR. It may be worthwhile to design a clinical study to assess effects of intravenous DR on hemodynamics in patients presenting with diastolic heart failure.

## Conclusion

Currently there are no approved effective treatments for diastolic dysfunction; however, the findings from this pilot study demonstrate some trends for the potential use of DR in treatment of patients with diastolic heart failure. However, due to the limited number of patients in this study, as well as the short duration of treatment and follow-up, future studies are necessary to substantiate these positive benefits of DR as a potential agent in the treatment of diastolic heart failure.

## Funding

Bioenergy, Inc., Minneapolis, MN, USA provided an Unlimited Educational Research Grant to study the effects of D-ribose in diastolic dysfunction in heart failure patients as a pilot study.

## Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

## References

Acil, T., Wichter, T., Stypmann, J., Janssen, F., Paul, M., Grude, M. *et al.* (2005) Prognostic valve of tissue Doppler imaging in patients with chronic congestive heart failure. *Int J Cardiol* 103: 175–181.

Bursi, R., Weston, S., Redfield, M., Jacobsen, S., Pakhomov, S., Nkomo, V. *et al.* (2006) Systolic and diastolic heart failure in the community *J Am Med Assoc* 296: 2259–2260.

Hegewald, M., Palac, R., Angello, D., Perlmutter, N. and Wilson, R. (1991) Ribose infusion accelerates thallium redistribution with early imaging compared with late 24-hour imaging without ribose. *J Am Col Cardiol* 18: 1671–1681.

Ibel, H. and Zimmer, H. (1986) Metabolic recovery following temporary regional myocardial ischemia in the rat. *J Mol Cell Cardiol* 18(Suppl. 4): 61–65.

Ingwall, J. and Weiss, R. (2004) Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circ Res* 95: 135–134.

Kriett, J., Ward, H., Bianco, R., Einzig, S., Alyono, D., Anderson, R. *et al.* (1983) Recovery of adenine nucleotides and cardiac function following ischemia. *Circulation* 68: III–389.

Omran, H., Illien, S., MacCarter, D., St Cyr, J. and Luderitz, B. (2003) D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. *Eur J Heart Fail* 5: 615–619.

Perkowski, D., Wagner, S., Marcus, A. and St Cyr, J. (2007) D-Ribose improves cardiac indices in patients undergoing 'off' pump coronary arterial revascularization. *J Surg Res* 137: 295.

Perlmutter, N., Wilson, R., Angello, D., Palac, R., Lin, J. and Brown, B. (1991) Ribose facilitates thallium-201 redistribution in patients with coronary artery disease. *J Nuc Med* 32: 193–200.

Pliml, W., von Arnim, T., Stäblein, A., Hofmann, H., Zimmer, H. and Erdmann, E. (1992) Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. *Lancet* 340: 507–510.

Sawada, S., Lewis, S., Kovacs, R., Khouri, S., Gradus-Pizlo, I., St Cyr, J. *et al.* . (2009) Evaluation of the anti-ischemic effects of D-ribose during dobutamine stress echocardiography: a pilot study. *Cardiovasc Ultrasound* 7: 7120–7127.

Schneider, J., St Cyr, J., Mahoney, J., Bianco, R., Ring, W. and Foker, J. (1985) Recovery of ATP and return of function after global ischemia. *Circulation* 72: Suppl III–298.

Shmuylovich, L. and Kovacs, S. (2007) E-wave deceleration time may not provide an accurate determination of LV chamber stiffness if LV relaxation/viscoelasticity is unknown. *Am J Physiol Heart Circ Physiol* 292: H2712–H2720.

St Cyr, J., Bianco, R., Schneider, J., Mahoney, J., Tveter, K., Einzig, S. *et al.* (1989) Enhanced high energy phosphate recovery with ribose infusion after global myocardial ischemia in a canine model. *J Surg Res* 46: 157–162.

Tveter, K., St Cyr, J., Schneider, J., Bianco, R. and Foker, J. (1988) Enhanced recovery of diastolic function after global myocardial ischemia in the intact animal. *Pediatr Res* 23: 226A.

Ward, H., St Cyr, J., Cogordan, J, Alyono, D., Bianco, R., Kriett, J. *et al*. (1984) Recovery of adenine nucleotide levels after global myocardial ischemia in dogs. *Surgery* 96: 248–255.

Zile, M. and Brutsaert, D. (2002) New concepts in diastolic dysfunction and diastolic heart failure: part II. Causal mechanisms and treatment. *Circulation* 105: 1503–1508.

Zimmer, H. and Ibel, H. (1984) Ribose accelerates the repletion of the ATP pool during recovery from reversible ischemia of the rat myocardium. *J Mol Cell Cardiol* 16: 863–866.