

A Potential Role of D-Ribose for Myocardial Diastolic Dysfunction

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ABSTRACT

Myocardial diastolic dysfunction can occur in patients with cardiovascular disease, as well as in the normal population. D-ribose, a pentose carbohydrate, has been shown to aid in the recovery of energy compounds and improve diastolic dysfunction in the ischemic myocardium. Presently, there is no significant effective approved therapy directed at improving this functional abnormality; and therefore, D-ribose may offer a benefit to individuals afflicted with diastolic dysfunction.

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Key words: Diastolic dysfunction; ATP; Ischemia; D-ribose

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EDITORIAL

Diastolic dysfunction is an abnormality in the functional relaxation phase of the heart. This abnormality has been observed in clinical presentations, such as following a myocardial infarction, as well as in many patients with congestive heart failure. Paulus *et al* defined diastolic dysfunction as a slowing in left ventricular relaxation and an

increase in left ventricular stiffness. Diastolic dysfunction can occur even with relatively normal systolic function or normal ejection fraction^[1].

Besides these overt clinical presentations, Redfield *et al* reported that this abnormality can be observed in normal individuals. They reported, in assessing 2042 randomly selected adults over the age of 45, that 21% had mild diastolic dysfunction, 7% had at least moderate diastolic dysfunction, and 6% had moderate or severe diastolic dysfunction with a normal ejection fraction^[2]. Other researchers have found similar findings of diastolic dysfunction in healthy individuals. Fisher *et al* found diastolic dysfunction in 2.8% of individuals between 25-35 years of age and 15.8% among individuals older than 65 years of age. When comparing genders, men had a higher rate of diastolic abnormalities (13.8% vs. 8.6% in women)^[3]. Presently there is no significantly effective approved therapy directed at improving diastolic dysfunction.

Every cell requires adequate levels of adenosine triphosphate (ATP) to maintain its integrity and function. Normally, this demand versus supply relationship is achieved; however, conditions can evolve where demand exceeds supply. Ischemia produces depletion in these essential high energy molecules with a subsequent effect in potentially compromising organ function. Myocardial ischemia produces a reduction in ATP levels with the potential to alter myocardial function, predominantly in diastole. Intracellular calcium with adequate intracellular energy levels plays a major role in maintaining diastolic function. Adenosine triphosphate provides the energy for the interaction between cytosolic calcium and the sarcoplasmic reticulum. Depleted or inadequate ATP levels can result in calcium remaining fixed to troponin longer in diastole, producing a dysfunctional state or altered ventricular compliance^[4]. Theoretically, methods directed at preserving or maximizing the recovery of myocardial ATP levels in states of ischemia could potentially aid in maintaining or improving diastolic function of the heart.

Pre-clinical evaluations directed at improving diastolic dysfunction have included in situ preparations, as well as both acute and chronic *in vivo* animal models. In a chronic canine model involving 20 minutes of normothermic, myocardial ischemia, there was a significant 50% decrease in myocardial ATP levels, as well as the development of left ventricular diastolic dysfunction

following this ischemic insult^[5]. Ward *et al* proposed that myocardial adenine nucleotide precursor availability is an important limiting factor in the recovery of myocardial ATP molecules following ischemia^[6]. Adenine nucleotide precursor supplementation, such as supplementation with the following substrates: adenosine, 5-amino-4-imidazolecarboxamide riboside, inosine, adenine, D-ribose, as well as adenine degradative enzymatic inhibitors, have been investigated for their potential role in recovering high energy phosphates following myocardial ischemia; however, mixed results in effectively replenishing ATP levels have been reported with many of these supplements. However, D-ribose, a natural occurring pentose carbohydrate, demonstrated in both pre-clinical and subsequent clinical studies its bioenergetics and functional benefits. Schneider *et al* reported that supplementation with D-ribose and adenine resulted in an improvement in ATP levels, as well as an improvement in left ventricular compliance/diastolic dysfunction following 20 minutes of normothermic, global myocardial ischemia in a canine model^[7]. Tveter *et al* found that when supplementing D-ribose alone following 20 minutes of normothermic myocardial ischemia in a canine model, there were similar benefits in both the restoration of ATP levels and an improvement in myocardial diastolic dysfunction, as previously reported with adenine and D-ribose by Schneider *et al*^[7,8].

Myocardial ischemia is a common entity in the development of congestive heart failure with many of these afflicted patients experiencing a degree of diastolic dysfunction. Clinically, these patients have a challenging therapeutic course, which can affect their prognosis^[9]. Ingwall and Weiss promoted that the failing heart is energy starved. This theory was previously proposed; however, it was not actively pursued due to the fact that it was unclear if ATP levels really decreased and if these levels did decrease in this disease, the remaining pool of ATP should be adequate to satisfy cellular energy requiring reactions^[10]. Currently, this energy deficiency theory in heart failure has gained momentum. Omran *et al* investigated the potential role of D-ribose for bioenergetics and functional benefits in patients with congestive heart failure, NYHA class II-III. He reported both objective and subjective improvements. Supplementation with oral D-ribose resulted in an enhancement in left atrial contribution to left ventricular filling, a smaller left atrial dimension and a shortened E wave deceleration by echocardiography. Subjectively, these patients experienced an improved quality of life and physical function as assessed by questionnaires^[11].

Congestive heart failure patients commonly complain of shortness of breath and fatigue. As their failure progresses, patients often experience an increase in these symptoms with a decrease in their ventilatory efficiency. Carter *et al* reported that the supplementation of D-ribose in 14 patients with heart failure, NYHA class II-III with left ventricular dysfunction, significantly maintained VO₂ max while improving VE/VCO₂, signifying a maintenance in maximal exercise capacity while improving ventilator efficiency, a strong predictor of heart failure survival in NYHA class II-III patients^[12].

Cardiovascular disease is the leading cause of deaths worldwide. Novel pharmaceuticals, medical foods, supplements, as well as devices, should be strongly pursued to decrease this death rate and improve a patients quality of life. Many individuals may experience a degree of diastolic dysfunction, potentially limiting their functional capacity. Presently, there is not an approved pharmaceutical or device that can offer an improvement in diastolic dysfunction; however, preclinical and clinical data using D-ribose appears to show promise in enhancing the recovery of cellular energy levels, as well as improving diastolic dysfunction in the ischemic myocardium.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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