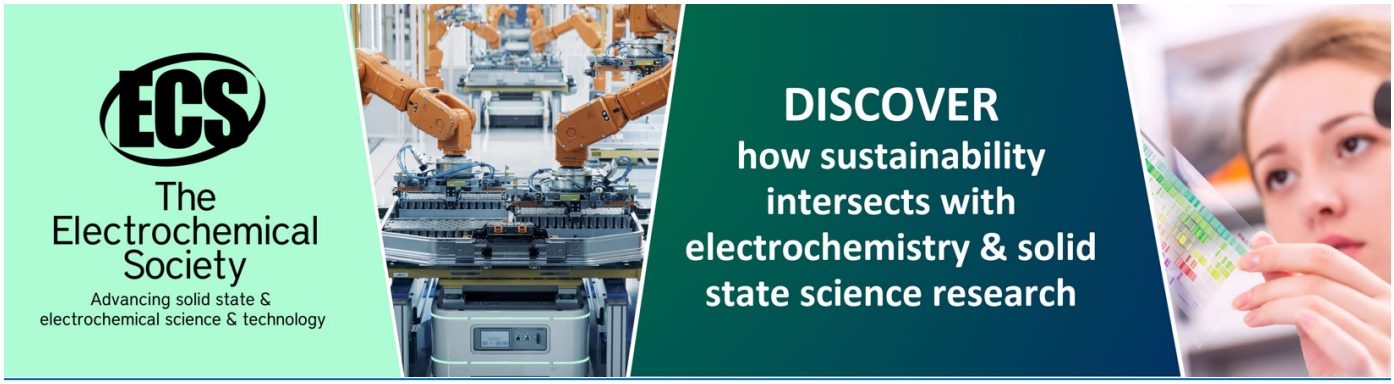
The Clinical Benefit of D-ribose in Cardiovascular Ischemic Disease: A New Potential Energy Supplement



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The Clinical Benefit of D-ribose in Cardiovascular Ischemic Disease: A New Potential Energy Supplement

I Damanik[1] and D Soemantri[1,2*]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Cardiology and Vascular Medicine, Dr. Soetomo General Hospital, Surabaya Indonesia

*Corresponding author : djokosoemantri2507@gmail.com

Abstract. Cardiovascular disease is still the leading cause of death worldwide. Atherosclerosis is the most common type of cardiovascular disease and can be caused by various factors, such as genetics and lifestyle. Cells need energy to maintain their integrity and function. Energy that is often used is adenosine triphosphate (ATP). Atherosclerosis can cause myocardial ischemia and induced reduction of ATP levels, so that that not only affects cellular energy, but also alters the normal function. D-ribose is a pentose carbohydrate that has been shown to increase cellular energy levels and improve function after ischemia in pre-clinical studies. It has shown potential benefits in clinical evaluation. This article aims to explain the role of D-ribose in increasing energy levels and myocardial function in ischemic cardiovascular disease.

1. Introduction

Cardiovascular disease is still the main cause of death worldwide. According to the *Center for Disease Control and Prevention*, about 61 million people suffer from heart disease in the United States. World Health Organization (WHO) reports that around 29% of all deaths in the world are related to heart disease. Atherosclerosis or the formation of plaques in the tunica intima of the arteries can be caused by various factors such as genetics and lifestyle. Lifestyle modification includes healthy diet consumption, stop smoking, control hypertension, increase physical activity, and stress management. Efforts to change lifestyle can have a positive impact on the potential to abridge cardiovascular risk events.

Plaque formation in coronary arteries can restrict the blood flow and oxygen to the tissues. Atherosclerosis is not limited to one area, but it is a systemic disease that can involve various organs such as the heart, peripheral circulation, and cerebrovascular. Significant coronary artery atherosclerosis can cause angina or chest pain symptoms. Usually, angina arises during and after experiencing a stressful situation, but, in some patients, symptoms can happen at rest. Coronary artery disease (CAD) involves formation of an atherosclerotic plaque, patient will become more susceptible to get acute or chronic myocardial infarction, which, over some time, can potentially progress into congestive heart failure (CHF). Coronary artery ischemia with longstanding hypertension may cause diastolic dysfunction and myocardial abnormalities in ventricular relaxation period. Ventricular dysfunction is still a clinical problem until now because it is only treated with therapy [1].

Many studies have found that the incidence of left ventricular (LV) diastolic dysfunction is quite high. Redfield *et al.*, stated that systolic dysfunction often occurs in individuals without CHF. Diastolic

dysfunction is more general, often not accompanied with CHF and associated with an increase in all causes of mortality. One study chose adults over the age of 45 years randomly, and found 21% of sample had mild diastolic dysfunction, 7% had moderate diastolic dysfunction moderate, and 6% had moderate to severe diastolic dysfunction [2].

Myocardial ischemia is a common underlying cause of CHF and many of the patients also experience diastolic dysfunction. Clinically, 50% of CHF patients will have varying degrees of diastolic dysfunction or have combination with systolic dysfunction. Myocardial ischemia alters the cellular metabolism; it can be seen in lower levels of adenosine triphosphate (ATP). Ingwall and Weiss proposed that the cause of heart failure was lack of high energy phosphate [3].

2. Cell Bioenergetics and Function

Every cell needs high energy phosphate levels which are sufficient to maintain cell integrity and its function. This cellular energy supply, ATP, usually meets the body demand. ATP is produced by intracellular pathways, such as glycolysis and tricarboxylic acid cycle, with glucose as initial substrate. But some cells can also rely on alternative pathways for ATP production, such as the pentose phosphate pathway [4]. There is a direct relationship between development of ventricular diastolic dysfunction and adequate myocardial ATP levels. Calcium plays a major role in this interaction. ATP provides energy for interactions between arcoplasmic reticulum and cytosolic calcium. Depletion of ATP may lead to calcium remains in troponin longer in the diastolic phase. It may lead to diastolic dysfunction or change ventricles' compliance.

When cells experience ischemia or hypoxia, the normal production of energy compounds will be reduced. Myocardial ischemia depletes ATP levels, affecting intracellular reactions and cell function. If the degree of ischemia is severe enough, cell survival will be threatened. The researchers also found that the effect of acute and chronic decrement of ATP levels in the myocardium after ischemia may last for a period because the synthesis of adenine nucleotides is slow. Zimmer *et al*. report that recovery of myocardial energy levels as an improvement in mechanical function during ischemia needs a long period [5]. Many studies of ischemic myocardium involve "isolated heart". Short-term investigations with animal models found similar findings at the myocardium adenine nucleotide level after ischemia. It is also reported that the state of 12- 30 minutes myocardial ischemia resulted in a significant decrease in ATP levels with decreasing in total adenine nucleotides and with a few days needed for a total recovery [6].

3. Metabolism of Adenine Nucleotides and D-ribose

Ward *et al*. stated that the availability of myocardial precursors is an essential factor in myocardial ATP molecules recovery after ischemia [7]. Catabolism of adenine nucleotides produces precursors that can be lost from cells, thereby inhibiting ATP recovery (Figure 1).

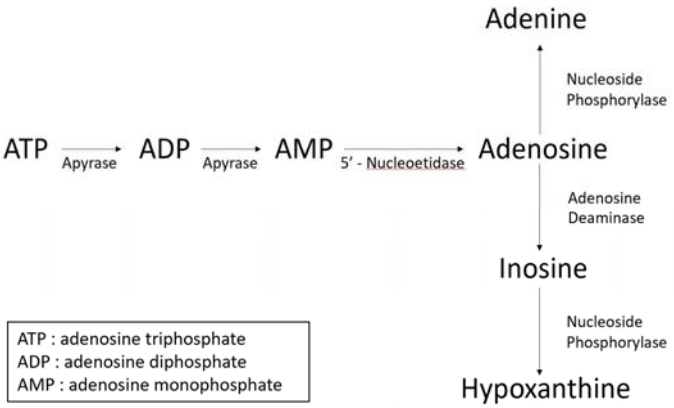

Figure 1 Adenine nucleotides catabolism

The levels of ATP myocytes after ischemia depend on the availability of precursor phosphoribosyl-pyrophosphate (PRPP), and D-ribose has been proven to induce nucleotides synthesize faster by increasing levels of PRPP directly [5]. Various adenine nucleotides have been investigated to replenish low post-ischemic myocardial ATP depletion, such as 5-amino-4-imidazole carboxamide riboside, adenosine, inosine, adenine, and D-ribose. Not only are the precursors evaluated, but also the use of adenine inhibitor degradation enzymes for carriers or rapid filling energy levels during ischemia. However, D-ribose supplementation has been proven to offer great benefits. D-ribose has been tested repeatedly in numerous studies on animals. D-ribose has a significant advantage in increasing levels of ATP and diastolic function when myocardial ischemia occurred.

4. D-ribose metabolism

D-ribose can produce nucleotides and metabolic intermediaries, such as ribose-5-phosphate. As shown in Figure 2, ribose-5-phosphate is an important intermediate in the pentose phosphate pathway, also known as the hexose monophosphate shunt or phosphogluconate pathway.

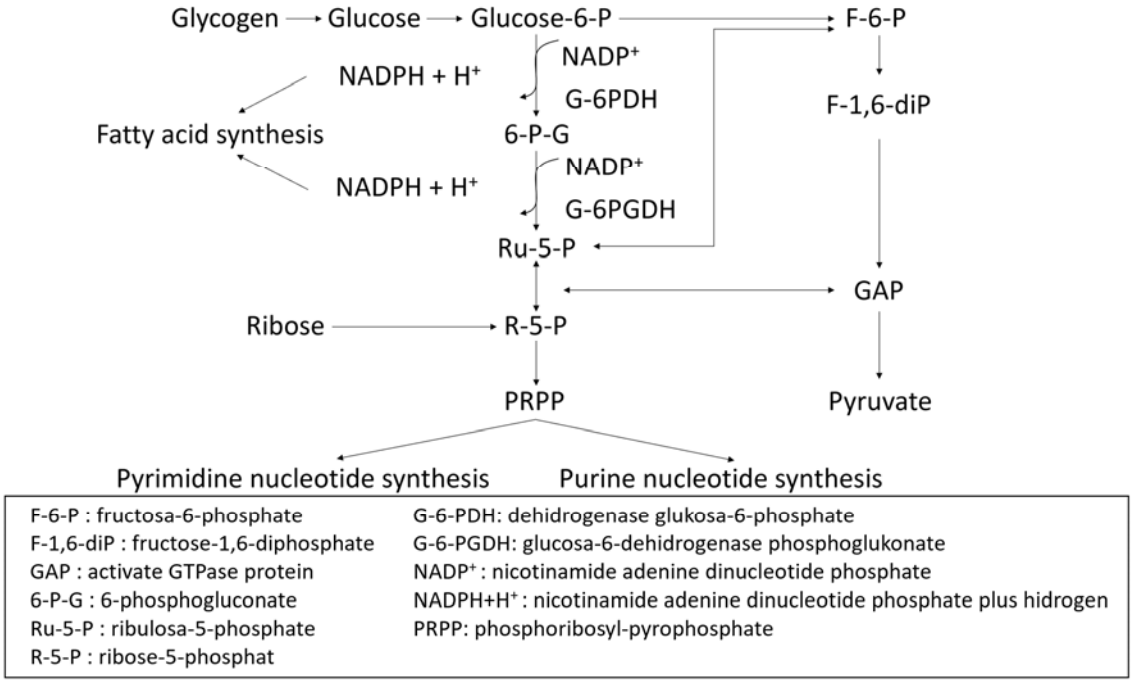

Figure 2. Pentose phosphate pathway

Ribose enters the pentose phosphate pathway by being phosphorylated into ribose-5-phosphate by ribokinase. Ribose-5-phosphate can be used on different paths, glucose synthesis, glycolysis, and in the synthesis of pyrimidine nucleotides or purine nucleotides. Ribose is a substrate for the formation of PRPP, a precursor for *de novo* ATP synthesis (Figure 3).

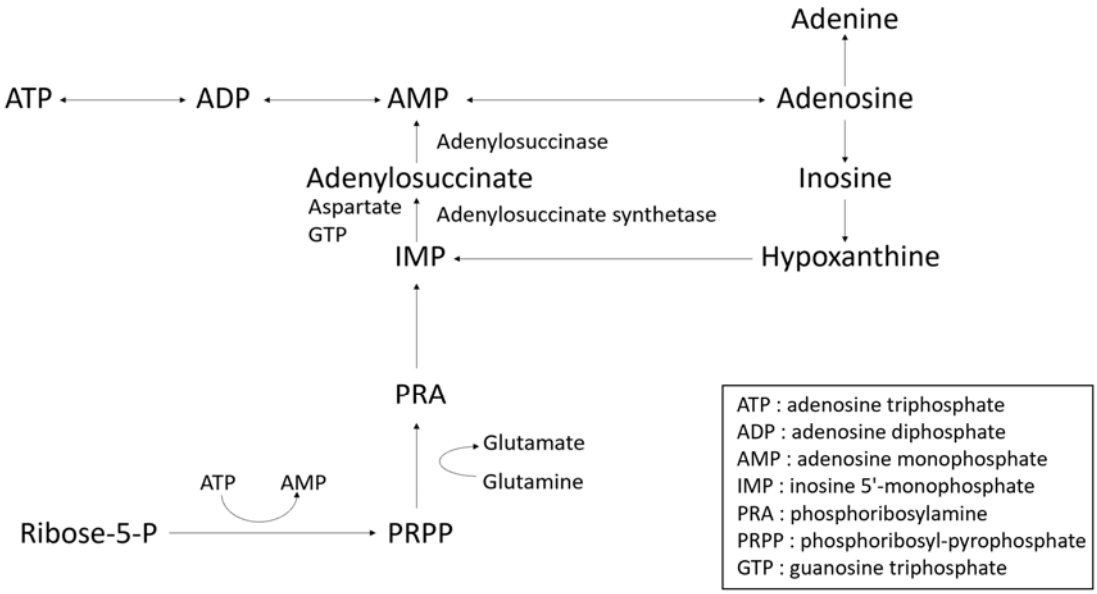

Figure 3. *de novo* pathway

On *de novo* pathway, the nucleotide bases are assembled from simple compounds and then attached to the ribose molecule, while, in salvage pathway, nucleotides are synthesized by recycling intermediates in the path of degradative for nucleotides (Figure 4).

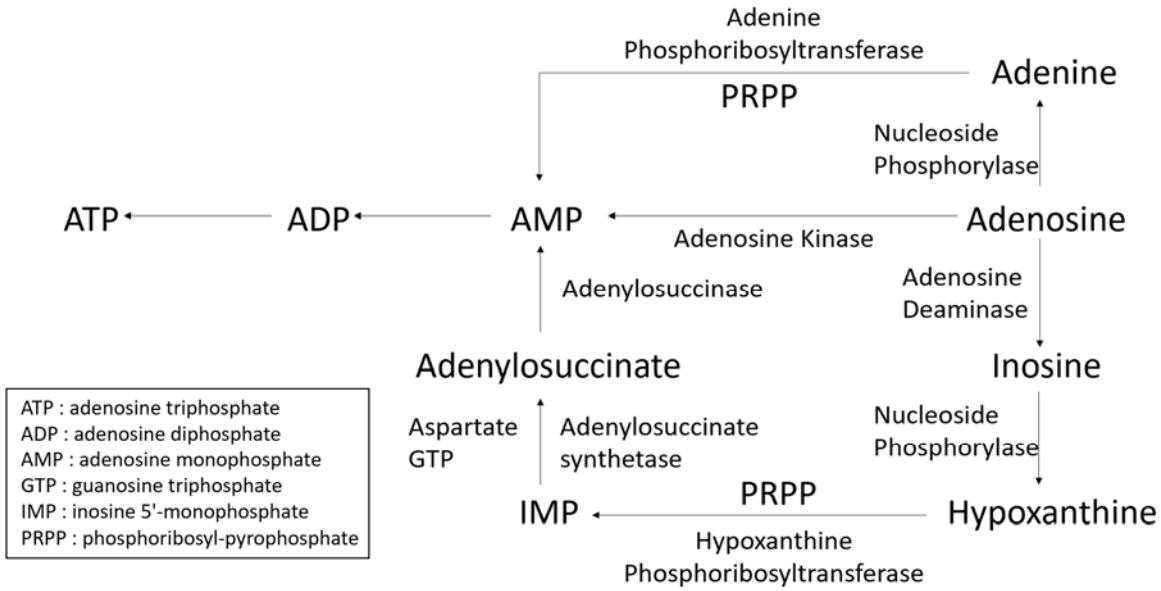

Figure 4. Salvage pathway

There is a reciprocal relationship between *de novo* pathway and escape in the PRPP holds an important role. Ribose plays an essential role in myocardial metabolism, largely via participation in the formation of PRPP leading to adenine nucleotide synthesis, especially ATP. The ribose supplement has specificity because it passes through an enzymatic step that limits the rate of the pentose phosphate pathway, glucose-6-phosphate dehydrogenase, thus directly increasing PRPP level which leads to an increase in the

production of myocardial adenine nucleotide biosynthesis. This process produces ATP molecules at an enhanced level so that they offer benefits not only in cell bioenergy status, but also in the functional aspects of the cell.

5. Benefit of D-ribose

In study in isolated adult hearts, D-ribose supplements produce an increase in the rate of adenine nucleotide synthesis when ischemia occurs. Also reported are similar results in the heart of isolated rats and ischemic perforations for 15 minutes. D-ribose supplementation improves myocardial ATP levels recovery, as well as increased functional recovery after ischemia [8]. Using the dog as animal model, Bianco *et al.* reported on the advantages of supplements D-ribose when used with adenine, resulting in the returning of 85% of levels of ATP in 24 hours [9]. In a separate study using an in vivo research model in dogs, Schneider *et al.* found the benefits of a similar ATP by supplementing D-ribose and supplemental adenine after twenty minutes from global myocardial ischemia, with improvements of LV diastolic dysfunction.

Zimmer *et al.* found a progressive reduction in LV systolic pressure, decreased dP / dT max left ventricle, increased LV end-diastolic pressure, cardiac output, and lower stroke volume in post-infarction patient. D -ribose supplementation after infarction increases hemodynamic parameters in these symptoms as measured by stimulation of adenine nucleotide synthesis. Similar findings were also obtained when Befera *et al.* administered D-ribose after acute myocardial infarction in adult mice. There was an increase in LV contractility and myocardial wall thickness with less ventricular dilatation in the area of LV myocardial infarction.

Myocardial hibernation is a regional area of myocardial dysfunction that is caused by prolonged hypoperfusion or ischemia. Theoretically, a Thallium-201 scan, magnetic resonance imaging, positron emission tomography, and dobutamine stress echocardiography can help in the identification of this area in the myocardium by providing useful information in management strategies for revascularization. Myocardial hibernation is associated with lowering of ATP level. Supplementation nucleotides adenine agents, such as D-ribose, can help identify what is still viable area. The D-ribose supplementation had anti-ischemic effects by increasing the identification of abnormalities in ventricular wall dysfunction found during dobutamine stress echocardiography [10].

Pliml *et al.* found a significant decrement of ATP level in ischemic myocardium. Supplementing D-ribose has a potential role in increasing the ATP level especially in patients with ischemic coronary artery. They examined D-ribose supplementation in patients with stable coronary artery disease using a serial treadmill exercise test. Supplementation D-ribose showed benefits by significantly improving treadmill exercise results before ischemic electrocardiographic change and onset of angina during exercise [11].

Long-term myocardial ischemia plays an important role in the development of CHF. Past studies in clinical animals have shown that D-ribose supplementation improves myocardial ATP recovery levels and increases diastolic dysfunction after ischemia. One study explored the role of D-ribose supplementation CHF patients. They found an increase in echocardiographic parameters in diastolic dysfunction. In that study, the results showed increased atrial filling into the left ventricle, smaller left atrial space size, and shortened E wave deceleration. Patients also experienced an improvement in quality of life and physical ability [12]. A recent study showed improvement in Doppler tissue velocity improvement, which was maintained at nine weeks in 64% of class II-IV CHF when receiving D-ribose supplementation. About 45% showed an increase in the initial diastolic filling speed (E) toward the initial relaxation annulus velocity (E'). Generally, CHF patients complain of fatigue and shortness of breath and, as this condition continues, patients experience decreasing in ventilation efficiency. D-ribose supplementation allows CHF class II-III patients with LV dysfunction to maintain maximal oxygen volume (VO2 max), improve ventilation efficiency, and has positive trends in improving measurement of their quality of life. Other study agreed with the reported benefits of D-ribose in a separate clinical study involving CHF class II-IV patients when receiving D-ribose supplementation. Clinically there was a significant improvement of ventilation efficiency in CHF class III-IV patients.

6. Conclusions

Cardiovascular disease is still ranked as the leading cause of death worldwide, even with rapid advances in cardiovascular therapeutic technology. Myocardial ischemia is commonly found in cardiovascular disease, playing a major role in the majority of deaths. Cells need high-energy phosphate levels that are sufficient to maintain cell integrity and function. Numerous studies have shown that myocardial ischemia decreases ATP levels, which can be reflected in changes in diastolic function. D-ribose, a naturally occurring pentose carbohydrate. Many pre-clinical studies and clinical studies show increased recovery of ATP levels to help prevent left ventricular diastolic dysfunction after ischemia. These studies also show potential clinical benefits in acute and chronic myocardial ischemic conditions, improved identification of myocardial hibernation, and improved functional parameters in patient with congestive heart failure.

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