



The Open Cardiovascular Medicine Journal

Content list available at: www.benthamopen.com/TOCMJ/

DOI: 10.2174/1874192401610010158



REVIEW ARTICLE

Impaired Myocardial Bioenergetics in HFpEF and the Role of Antioxidants

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Received: February 3, 2016

Revised: June 10, 2016

Accepted: June 10, 2016

Abstract: Heart failure with preserved ejection fraction (HFpEF) is a significant cardiovascular condition for more than 50% of patients with heart failure. Currently, there is no effective treatment to decrease morbidity and mortality rates associated with HFpEF because of its pathophysiological heterogeneity. Recent evidence shows that deficiency in myocardial bioenergetics is one of the key pathophysiological factors contributing to diastolic dysfunction in HFpEF. Another known mechanism for HFpEF is an overproduction of free radicals, specifically reactive oxygen species. To reduce free radical formation, antioxidants are often used. This article is a summative review of the recent relevant literature that addresses cardiac bioenergetics, deficiency in myocardial bioenergetics, and increased reactive oxygen species associated with HFpEF and the promising potential use of antioxidants in managing this condition.

Keywords: Adenosine triphosphate, Antioxidants, Bioenergetics, Diastolic heart failure, Free radicals, Heart failure with preserved ejection fraction.

1. BACKGROUND

Heart failure (HF) is a serious, progressive cardiovascular disease in which the myocardium is unable to pump sufficient blood to meet the body's demand. In the United States, approximately 5.1 million people have HF which is estimated to cost the nation about \$32 billion each year.

An individual with HF has problems related to functional or structural impairment of ventricular filling or ejection of blood from the heart. Patients with HF are often classified based on ejection fraction (EF) in terms of either preserved or reduced EF. Thus, systolic HF is referred to as heart failure with reduced ejection fraction (HFrEF), and diastolic HF is referred to as heart failure with preserved ejection fraction (HFpEF) [1]. Approximately 50% of the patients with HF have HFpEF and they have higher morbidity and mortality rates than patients with HFrEF. Some clinicians believe that HFpEF is an emerging epidemic because of the rising prevalence in patients over the age of 65 and the lack of treatment for impaired myocardial energy availability [2].

The most recent guidelines related to the management of HF were published in 2013 by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA). This document includes discussion about the challenge of diagnosing patients with HFpEF because of the many causes of their symptoms; however, there is no mention of myocardial bioenergetics. There is a brief discussion of nutritional supplements and hormonal therapies but it is suggested that more data are needed before recommendations for HFpEF treatment are made [1].

For patients with HFpEF activation of the sympathetic nervous system and the renin angiotensin system can cause elevation in the production of free radicals, particularly reactive oxygen species (ROS) in the myocardium. This increase in ROS leads to excess oxidative stress that damages the myocardium. In addition to the increase in ROS,

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impairment of the mitochondrial bioenergetics leads to decreased adenosine triphosphate (ATP) production [3]. Both of these factors are now believed to be major mechanisms for the development of HFpEF [4 - 6]. In this article we will specifically review how increasing myocardial bioenergetics and supplementing antioxidants are potential additional treatments for HFpEF.

2. MYOCARDIAL BIOENERGETICS

Bioenergetics is a broad term used to describe energy transactions and transformations [7]. Compared to cells in any other organ, cell in the myocardium consume the most energy. Although the myocardium can generate ATP utilizing a variety of substrates, the vast majority of ATP is synthesized in the electron transport chain (ETC) of mitochondria in the form of ATP or phosphocreatine (PCr). The myocardial consumption of ATP is approximately 1 nM ATP per second, and myocardial energy stores must be regenerated about every 20 seconds in order to meet the high demand for ATP in the heart [8]. Relevant to HFpEF, diastolic myocardial consumption of ATP exceeds systolic ATP consumption [9].

An important component of myocardial energetics is calcium, which plays a role in the regulation of ATP synthesis and in consumption associated with myocardial contraction and relaxation [10]. During excitation-contraction, calcium is released from the sarcoplasmic reticulum and then binds to troponin C, causing displacement of tropomyosin and allowing actin-myosin cross-bridging. The thick and thin filaments of the sarcomere are then able to slide past each other, resulting in cardiac muscle contraction. In contrast, reuptake of calcium back to the sarcoplasmic reticulum contributes to the relaxation of cardiac muscle, an active process requiring ATP. In HFpEF, there is a leak and impaired uptake of calcium that leads to profound alterations in cardiac contractility [11].

There are significant changes in the bioenergetics of the myocardial mitochondria with age. Over time, ROS damage occurs mainly in Complex I of the ETC within mitochondria [12]. This damage results in energy decline associated with impaired early diastolic filling. There is increased myocardial torsion to shortening ratio and a reduction in the PCr to ATP ratio. The consequence of these alterations in the myocardial mitochondria is the pathophysiologic basis of HFpEF [13]. Myocardial energy deficiency underlies the disruption of myocardial bioenergetics that leads to HFpEF [8].

3. REACTIVE OXYGEN SPECIES AND ANTIOXIDANTS

Free radicals are unstable and highly reactive molecules with unpaired electrons. These molecules can either accept or donate electrons from or to other molecules, and this produces either reductants or oxidants. Often the oxidant is termed a ROS to describe a superoxide ($O_2^{\bullet-}$) or hydroxyl radical (OH^{\bullet}). For proper physiologic balance there must be equilibrium between free radicals and antioxidants. If ROS are overproduced, they can damage parts of the cell such as the proteins, lipids, and DNA. When there is an overabundance of ROS and the body's antioxidant system is unable to regulate the free radicals, oxidative stress occurs [14, 15]. There is evidence suggesting that excessive oxidative stress causes damage to the myocardium in patients with HFpEF [16, 17].

In the cardiac myocytes, approximately 90% of the ATP is produced from the mitochondria. The mitochondria are a major source of ROS in the myocardium representing byproducts of oxidative phosphorylation. In myocardial mitochondria, the major $O_2^{\bullet-}$ is mainly produced by electron leakage from the ETC. A decrease in mitochondrial phosphorylation then increases electron leakage from the ETC and consequently produces hydrogen peroxide (H_2O_2) that is then converted to the highly damaging OH^{\bullet} . Consequently, there is oxidative stress from the overproduction of mitochondrial ROS that has been associated with many cardiac diseases including HFpEF [18].

Patients with HFpEF have elevated ROS levels that contributes to the hypertrophy and increased resting tension in cardiomyocytes [19]. In numerous studies researchers have investigated the various molecular pathways related to ROS production in HFpEF [20, 21]. Hirata *et al.* recently used a novel biomarker called derivatives of reactive oxidative metabolite (DROM) and found that increased DROM was an independent and significant predictor of cardiovascular events in HFpEF. Specifically there was an association between the increased DROM levels and severity of HFpEF [20]. This is an example of a potential useful biomarker to measure ROS concentrations in patients with HFpEF.

Using an antioxidant to counteract increased free radical production is a potential method to reduce myocardial injury in patients with HFpEF. In both animal [21, 22] and human studies researchers have investigated the effects of antioxidant therapy to improve myocardial function in HFpEF. Wilder *et al.* found in studies with mice that the oxidative myofilament modifications are an important mediator in diastolic function. They administered an antioxidant

called N-acetylcysteine (NAC) for 30 days and discovered that NAC reversed baseline diastolic dysfunction and hypertrophy [23]. However, many large clinical trials related to HF have failed to demonstrate a significant difference with antioxidants such as vitamin C or vitamin E [24]. This could be because these agents do not have a specific target for mitochondrial ROS generation. Thus, investigating antioxidant compounds such as coenzyme Q10 that target mitochondrial ROS is promising for future supplemental treatment of HFpEF [3]. A meta-analysis of coenzyme Q10 randomized clinical trials found that it improves outcomes of HF patients. Since coenzyme Q10 is an integral component of the mitochondrial respiratory chain for ATP production and also an antioxidant, coenzyme Q10 could assist in improving myocardial function in HF patients [25].

4. MANAGEMENT OF HFpEF

The principal symptoms of HFpEF include exertional shortness of breath and fatigue [26]. The majority of patients with HFpEF are older women with a history of hypertension. In addition, these patients have many comorbidities such as obesity, diabetes mellitus, dyslipidemia, and coronary artery disease [27, 28]. The 2013 ACCF/AHA Guideline for the Management of Heart Failure recommends the use of diuretics for symptoms of volume overload and beta-blocking agents, angiotensin-receptor enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARB) for hypertension [1]. Nevertheless, there are no pharmaceutical agents that have altered the clinical course of HFpEF.

Studies have indicated that moderate walking exercise for patients with HFpEF is associated with improved symptoms of fatigue and shortness of breath, and with weight loss and improved quality of life. However, exercise may not change the patient's systolic or diastolic function [29 - 31]. Adjunctive therapy such as omega-3 polyunsaturated fatty acids [32, 33], coenzyme Q10 [34], and D-ribose [35] supplementation have been found useful for reducing the symptoms of HFpEF. Further research is needed because the recommended management of HFpEF has not been effective in reversing the poor prognosis for these patients. The absence of effective therapeutic strategies may be related to the heterogeneity of HFpEF pathophysiology and to inadequate emphasis placed on myocardial bioenergetics.

Below is a summary of the key messages expressed in this article (Table 1).

Table 1. Key messages.

• HFpEF activates sympathetic nervous system and the renin angiotensin system causing increased free radical production.
• There are currently no pharmaceutical agents that have altered the clinical course of HFpEF.
• There is a decline in myocardial bioenergetics with aging.
• Patients with HFpEF have elevated reactive oxygen species (ROS) which impairs mitochondrial bioenergetics.
• Several antioxidants such as ubiquinol reduce ROS production and improve myocardial energetics.
• Antioxidant augmentation could potentially reduce the incidence of HFpEF.

CONCLUSION

Myocardial bioenergetics deficiency is proposed as one of the key underlying mechanisms contributing to the development of HFpEF in patients. This is supported by recent literature showing that enhancing myocardial bioenergetics could potentially be effective in reducing the incidence of HFpEF [36]. Additional research is needed to investigate the effects of using antioxidants (*e.g.*, coenzyme Q10) to assist with the insufficient cardiac bioenergetics in HFpEF. The use of antioxidant therapies could be a potential supplemental treatment in patients with HFpEF that would optimize their overall health.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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