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Review Article

Myocardial energetics and ubiquinol in diastolic heart failure

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Abstract Diastolic heart failure, or heart failure with preserved ejection fraction, is a leading cause of morbidity and mortality. There are no current therapies effective in improving outcomes for these patients. The aim of this article is to review the literature and examine the role of coenzyme Q_{10} in heart failure with preserved ejection fraction related to mitochondrial synthesis of adenosine triphosphate and reactive oxygen species production. The study results reflect that myocardial energetics alters in diastolic heart failure and that there is defective energy metabolism and increased oxidative stress. Studies are emerging to evaluate coenzyme Q_{10}, particularly ubiquinol, as a supplemental treatment for heart-failure patients. In diastolic heart-failure patients, clinicians are beginning to use supplemental therapies to improve patient outcomes, and one promising complementary treatment to improve left ventricular diastolic function is ubiquinol. Additional studies are needed using large-scale randomized models to confirm if ubiquinol would be beneficial. Since ubiquinol is an antioxidant and is required for adenosine triphosphate production, clinicians and health scientists should be aware of the potential role of this supplement in the treatment of diastolic heart failure.

Key words ATP, HFpEF, myocardial energetics, ubiquinol, heart disease, coronary artery disease.

INTRODUCTION

Heart failure (HF) is a heterogeneous, complex clinical syndrome in which the myocardial pump is insufficient to meet the body's demands for blood and oxygen (Roger *et al*., 2012). It is a chronic and progressive condition that results in pulmonary congestion and peripheral edema (Tsutsui *et al*., 2011). Despite advances in the management of HF and widespread application of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, HF remains a highly prevalent public health problem, especially within an aging population (Tsutsui *et al*., 2011). Worldwide, coronary heart disease is a leading cause of death among adults. Education can assist in improving the lives of patients with heart failure by changes in routine (Zhu *et al*., 2014). Even with initiatives on risk factor and symptom reduction, hospital 30-day readmission rates for HF remained consistently elevated (Quality AFHRA, 2012; Bogaev, 2010). The annual cost for direct and indirect care of those afflicted with HF and stroke is estimated to be approximately $312.6 billion (Go *et al*., 2013). These statistics and projections reveal the necessity of developing clinical measures to reduce the incidence of HF and to target those that may be at risk of developing the signs and symptoms of HF.

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A new approach is warranted to focus on the underlying mechanism(s) that lead to myocardial dysfunction, which can result in the development of HF. Evidence reveals that alterations in myocardial energetics, such as defective energy metabolism and increased oxidative stress, an excess production of reactive oxygen species (ROS) in relation to antioxidant defense is a significant factor in HF (Tsutsui *et al*., 2011). Studies are emerging to evaluate the effects of a potent antioxidant, ubiquinol – the active reduced form of CoQ_{10} – on the myocardium. In a small pilot study, Langsjoen and Langsjoen (2008) reported improvement of left ventricular (LV) function among patients with congestive heart failure from the use of supplemental ubiquinol. This article will review: (i) the role of myocardial energetics in maintaining cardiac function, especially diastolic function and impairment of which could lead to diastolic heart failure (DHF); and (ii) the use of supplemental ubiquinol for the potential treatment and prevention of DHF.

MYOCARDIAL ENERGETICS

Myocardial energetics involves mechanisms to produce important cellular processes to generate adenosine triphosphate (ATP), the primary energy source of the cell. Of all the vital organs the heart has the highest metabolic demand for ATP. The myocardium requires ATP for normal systolic and diastolic function – sarcomere contraction and

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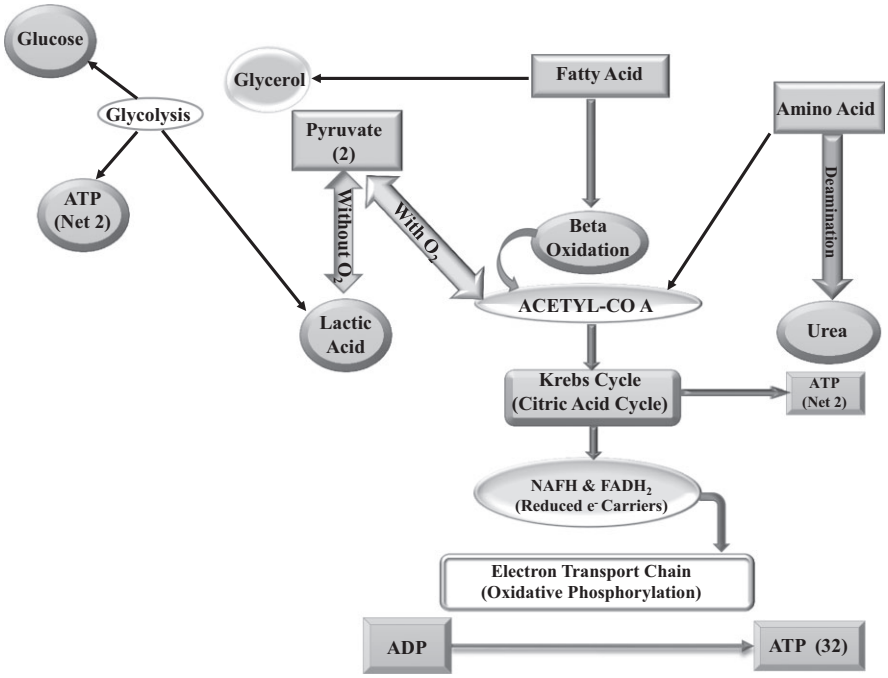

Figure 1. Normal cellular respiration pathways.

relaxation (Ingwall, 2009; Scolletta & Biagioli, 2010). In cardiac myocytes there are numerous mitochondria that are necessary for cellular respiration. Cellular respiration, as depicted in Figure 1, refers to the biochemical pathway by which cells release energy from the chemical bonds of food molecules and provide energy for cell function. Part of cellular respiration is ATP synthesis, which involves: (i) aerobic system (glycolysis, Krebs cycle, and oxidative phosphorylation); (ii) anaerobic system (lactic acid); and (iii) the phosphagen system, which consists of phosphocreatine (PCr) and, when synthesized, aids in the formation of ATP (Ingwall & Weiss, 2004; Scolletta & Biagioli, 2010).

To preserve cardiac performance, it is critically important to maintain a high ATP level (Ingwall, 2009; Scolletta & Biagioli, 2010; Furstenwerth, 2012). Approximately 90% of ATP is derived by oxidative phosphorylation via the electron transport chain (ETC), which is usually sufficient to maintain, even with fluctuations in cardiac workload (Postnov *et al*., 2007; Van Bilsen *et al*., 2009; Scolletta & Biagioli, 2010). Although the amount of ATP produced and used is greater than the amount of the ATP pool, the myocardium has the ability to synthesize the fats, carbohydrates, amino acids, triglycerides, and ketones that are storage forms of carbon-based fuels used for ATP synthesis. In conditions of myocardial stress, ATP demand may substantially exceed its supply, resulting in the consumption of ATP reserves from PCr via the creatine kinase reaction (Ingwall, 2009; Van Bilsen *et al*., 2009; Scolletta & Biagioli, 2010).

While oxidative phosphorylation is significant in cellular respiration for the production of ATP, it is also a major source of cellular ROS. A by-product of the ETC, ROS functions as a chemical messenger, and when produced in excess, can cause oxidative stress and mitochondrial dysfunction. Along with suppression of ATP synthesis, there is evidence that mitochondrial dysfunction results in oxidative stress, which directly affects the myocardial contractile function by altering myofibrils that are essential for excitation-contraction coupling (Tsutsui *et al*., 2011). In ROS, superoxide ($O_2^{-\bullet}$) is one of the major free radicals released from the myocardial mitochondria during oxidative stress. Free radicals, such as $O_2^{-\bullet}$ and hydroxyl (OH^-), have been implicated in many cardiovascular conditions. As ROS production is increased, a potent vasodilator, nitric oxide (NO), is decreased (Montezano & Touyz, 2012). In addition, $O_2^{-\bullet}$ reacts with elevated NO, forming a highly reactive oxidant peroxynitrite ($OONO^-$), which can further decrease mitochondrial energy production (Sheeran & Pepe, 2006; Tsutsui *et al*., 2011; Yu *et al*., 2012).

MYOCARDIAL ENERGETICS IN DIASTOLIC DYSFUNCTION AND HEART FAILURE

Studies have examined myocardial energetics and its relationship to diastolic dysfunction and HF (Tsutsui *et al*., 2011; Dai *et al*., 2012; Furstenwerth, 2012; Hollingsworth *et al*., 2012). Diastolic dysfunction refers to abnormal ventricular elasticity (compliance) during diastole, when the ventricle fills, both passively and actively. The increased resistance to the filling of one or both ventricles leads in turn to increased LV end-diastolic pressure (Satpathy *et al*., 2006; Lanier *et al*., 2012). It can occur with or without the presence of HF (Zile & Brutsaert, 2002; Satpathy *et al*., 2006). When diastolic dysfunction is present in the setting of a normal ejection fraction (≥ 50%) and there are accompanying signs and symptoms of

HF, it is characterized as diastolic HF, or HF with preserved ejection fraction (HFpEF) (Zile & Brutsaert, 2002). In contrast, when the myocardium has a reduced ejection fraction as a result of loss in contractility, accompanied with signs and symptoms of HF, it is referred to as systolic HF, or HF with reduced ejection fraction (HFrEF).

Ventricular relaxation is an energy-consuming process in which ATP hydrolysis is required for myofilament detachment and subsequent myocardial relaxation and elasticity (Zile & Brutsaert, 2002). Reduced levels of ATP and PCr have been observed when the heart starts to fail (Faller *et al*., 2013; Hollingsworth *et al*., 2012; Strumia *et al*., 2012). In addition, myocardial energetics can change with age without evidence of cardiovascular disease or hypertension. A review on mitochondrial changes in cardiovascular aging in mice revealed a significant decline in diastolic function with the increase of age (Dai *et al*., 2012). Hollingsworth *et al*. found that there is an increase in vascular stiffening in both men and women starting from the third decade in life, which can significantly affect LV function (Hollingsworth *et al*., 2012). This suggests that with normal aging the LV begins to have decreased myocardial energetics, which can start to impair early diastolic filling. Interstitial myocardial fibrosis occurs with aging and especially in significant myocardial stress such as aortic valvular stenosis. This process appears impervious to reversal by CoQ_{10} supplementation. Furthermore, since ATP and PCr are reduced in a failing myocardium, a low cardiac PCr/ATP may be the preferred predictor of cardiovascular mortality than the New York Heart Association (NYHA) Classification or LV ejection fraction (Faller *et al*., 2013; Strumia *et al*., 2012). Hence, when there is a diminished energy reserve, there is risk of a hypoxic insult that increases the patient's risk for acute mechanical failure. There are no randomized clinical trials regarding the treatment of CoQ_{10} for HFrEF. One study by Langsjoen and Langsjoen (2008) reflects significant improvement on systolic function and improved NYHA heart failure classification. There are no comparative studies of CoQ_{10} with beta-blockers, ACEI, or ARB in patients with HFrEF.

THE HYPERTENSION LINK

The application of current ACC/AHA guidelines has improved HF symptoms and measures of both mortality and morbidity in patients with HFrEF. In patients with HFpEF, HF symptoms may have been improved, but the evidence of decreased morbidity and/or mortality in randomized clinical trials continues to be lacking (Hunt *et al*., 2009). The focus of these also has been on the surveillance and treatment of hypertension, heart-rate control, and myocardial ischemia, all of which are known to adversely impact ventricular relaxation (Hunt *et al*., 2009).

Worsening diastolic dysfunction eventually leads to DHF, which has long been linked with hypertension (Martos *et al*., 2007). The primary focus of this article is not to address the causality of the complex nature of hypertension; nonetheless, we take note of the evidence suggesting that hypertension may not be the cause of diastolic dysfunction, but it may worsen the dysfunction and lead to HF. In a study by Dupont *et al*., spontaneously hypertensive rats (SHR) demonstrated early LV diastolic dysfunction before the onset of hypertension and LV hypertrophy (LVH) (Dupont *et al*., 2012). A Nigerian study on normotensive offspring of hypertensive parents revealed that diastolic dysfunction precedes clinical hypertension in genetically predisposed individuals, without evidence of LVH (Adeoye *et al*., 2012).

Mitochondrial dysfunction and catecholamine production may have a role in facilitating hypertension (Yu *et al*., 2012). In mitochondrial dysfunction there are decreased ATP synthesis, an augmented ROS, and decreased intrinsic antioxidants (Tsutsui *et al*., 2011; Dai *et al*., 2012). Experimental studies reveal that young SHR developed an increase in $O_2^{-\bullet}$ and oxidative stress prior to the manifestation of hypertension, suggesting that ROS are causally associated with hypertension (Postnov *et al*., 2007; Montezano & Touyz, 2012). Montezano and Touyz concluded that ROS plays an integral role in promoting the activation of the sympathetic nervous system, which is linked to elevation of blood pressure (Fig. 2) (Montezano & Touyz, 2012). Scolletta and Biagioli report that catecholamines, increased angiotensin II (a potent vasoconstrictor), and increased cardiac sympathetic tone, among other factors, influences mitochondrial ROS production (Scolletta & Biagioli, 2010). Tsuneki *et al*. noted that the relationship between ROS and angiotensin II involves a positive feedback mechanism that originates from the initial burst of ROS production (Fig. 2) (Tsuneki *et al*., 2013).

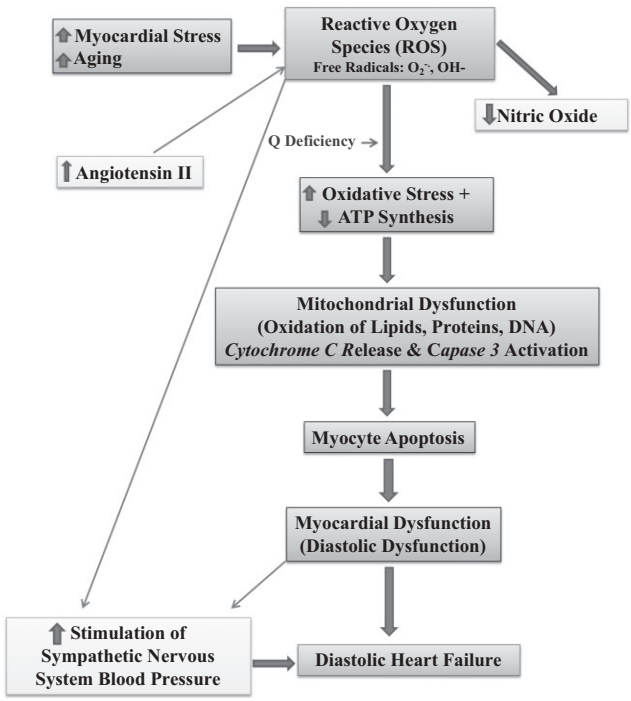

Figure 2. Scheme of myocardial energetics and ROS, CoQ_{10} deficiency, diastolic dysfunction, and stimulation of sympathetic nervous system resulting in diastolic heart failure.

COENZYME Q_{10}

Mitochondria are responsible for generation of both ROS and protective antioxidants, which are needed to combat excessive ROS. Such endogenous antioxidants include superoxide dismutase (SOD), glutathione, peroxidase, catalase, and ubiquinol (reduced form of CoQ_{10}). Antioxidants play important roles in catabolizing free radicals, as well as reducing the formation of and repairing damage caused in the cell structure. Ubiquinol, a potent antioxidant, has become a focus in various cardiovascular studies (Dai *et al*., 2012; Tsai *et al*., 2012; Fotino *et al*., 2013; Tsuneki *et al*., 2013). There are two major forms of coenzyme Q_{10} (CoQ_{10}) called ubiquinone and ubiquinol. These terms are often incorrectly used interchangeably. Ubiquinone is the fully oxidized lipid-soluble quinone present in all organs and is highly concentrated in the heart. Ubiquinol is the reduced form of CoQ_{10}, which is one of the most powerful antioxidants that prevent oxidative damage by free radicals (Fischer *et al*., 2012; Fotino *et al*., 2013; Tsuneki *et al*., 2013). CoQ_{10} is a key component in the ETC of the cellular respiratory process in the mitochondria (Fischer *et al*., 2012). The ETC contains complexes I through V. Electrons released from the Krebs cycle and donated to complexes I and II are transferred to ubiquinone and delivered to complex III, forming ubiquinol (Schmelzer & Doring, 2012; Yu *et al*., 2012).

Recent evidence supports the benefit of CoQ_{10} and its antioxidant effect against oxidative stress and endothelial dysfunction (Dai *et al*., 2012; Tsai *et al*., 2012; Tsuneki *et al*., 2013). Specifically, Tsai *et al*. demonstrated that CoQ_{10} suppressed the generation of ROS and inhibited inflammatory and oxidative damage in human endothelial cells (Tsai *et al*., 2012). The study also revealed that with CoQ_{10} there was: (i) a reduction in endothelin-1 (ET-1) secretion, which is responsible for vasoconstriction; and (ii) prevention of the release of cytochrome c, which when released, activates caspase 3 and leads to cellular apoptosis. Several randomized controlled studies have established an improvement in endothelial dysfunction with supplementation of CoQ_{10} in patients with coronary artery disease and type II diabetes (Dai *et al*., 2012; Tsai *et al*., 2012; Tsuneki *et al*., 2013). One study found that CoQ_{10} inhibited the upregulation of angiotensin II in the overproduction of ROS in human umbilical vein endothelial cells (Tsuneki *et al*., 2013). Tsai *et al*. noted that CoQ_{10} provides protection against oxidative stress and has the potential to prevent and treat HF (Tsai *et al*., 2012). However, in order for CoQ_{10} to be effective, it must be enzymatically maintained in its reduced form of ubiquinol (Tsuneki *et al*., 2013).

Researchers have reported that ubiquinone is not as readily absorbed as ubiquinol (Schmelzer & Doring, 2012). Langsjoen and Langsjoen studies revealed that patients had an increase in plasma CoQ_{10} when they were switched from ubiquinone to the stabilized ubiquinol, formulated by Kaneka Corporation of Japan (Langsjoen & Langsjoen, 2008). However, these investigators were not blinded and the project was funded by the Kaneka Corporation. Ubiquinol functions as a potent antioxidant found in the mitochondria, lipid membranes, and plasma lipoproteins, and is important for cellular functions such as DNA synthesis, repair, and stability (Fischer *et al*., 2012; Schmelzer & Doring, 2012). Ubiquinol has been described as an inhibitor of lipid peroxidation, which reduces damage to lipids, proteins, and DNA (Schmelzer & Doring, 2012). Ubiquinol also assists to regenerate other lipid soluble antioxidants, such as vitamin E (Fischer *et al*., 2012). Investigators have reported that ubiquinol reduces the inflammatory processes via gene expression in several *in vitro* studies in mice and humans (Fischer *et al*., 2012; Schmelzer & Doring, 2012). A clinical study found that supplementation with ubiquinol had a significant reduction of DNA damage in lymphocytes (Schmelzer & Doring, 2012). In addition, Fisher *et al*. discovered a reduction in DNA damage when ubiquinol was given. They found a decrease of LDL-cholesterol and erythropoiesis after ubiquinol supplementation and there were side-effects reported (Fischer *et al*., 2012). *In vivo* studies have reported that a plasma CoQ_{10} concentration greater than 3.5 mcg/mL is needed to achieve a beneficial effect (Shults *et al*., 1998; Ikematsu *et al*., 2006; Kumar *et al*., 2009). In 2007, ubiquinol became available to the public as a supplement. The highest plasma CoQ_{10} level reported was 9.3 mcg/mL, which was achieved using solubilized ubiquinol at a dose of 600 mg/day (Bhagavan & Chopra, 2007; Miles *et al*., 2007).

Individuals with HF have lower plasma and myocardial CoQ_{10} levels, which may correlate with the degree of HF in the NYHA classification. Langsjoen and Langsjoen (2008) found that there were subtherapeutic plasma CoQ_{10} levels in HF patients with class II and III of the NYHA scale, which is a reflection of functional limitations in patients with HF (Langsjoen & Langsjoen, 2008). Furthermore, the researchers report that supplemental ubiquinol therapy increased plasma CoQ_{10} levels, which may considerably improve diastolic dysfunction and lead to improvement in the NYHA class, regardless of significant changes in ejection fraction (Shaw, 2013).

The biosynthesis of CoQ_{10} is at its highest in the second decade of life, and decreases with aging beginning around age 40 (Bentinger *et al*., 2010; Tsai *et al*., 2012; Tsuneki *et al*., 2013). Mitochondrial production of ROS significantly increases in the myocardium with aging, escalating the risk of myocardial oxidative injury (Dai *et al*., 2012; Yu *et al*., 2012). As patients age, there is a decrease in the ability of the body to reduce ubiquinone to ubiquinol, resulting in oxidative stress, which leads to diastolic dysfunction, and subsequent DHF.

DIASTOLIC HEART FAILURE AND COENZYME Q_{10}

With the increasing number of over-the-counter CoQ_{10} supplements, it is difficult for clinicians and patients to know which product to purchase. Searching the Internet and reviewing the literature may not always be useful in resolving this dilemma. Our literature search utilizing multiple search engines revealed minimal results in the use of CoQ_{10} or ubiquinol in adults with diastolic dysfunction and/or DHF. There was marked variability in the dose and form of CoQ_{10} used in different studies. Early investigations often used low doses of CoQ_{10} and the less effective form of CoQ_{10} (ubiquinone) in older subjects. However, more recent experimental studies have found ubiquinol to be beneficial in

patients with HF, coronary artery disease, CHF, systolic hypertension, and inflammation (Littarru & Tiano, 2010; Dai *et al*., 2012; Fischer *et al*., 2012; Tsuneki *et al*., 2013). Randomized clinical trials are necessary to determine the effects of ubiquinol on HF (both HFpEF and HFrEF).

Diastolic heart failure is a significant contributor to the HF syndrome leading to morbidity, hospitalizations, and death. Approximately 5.7 million people in the United States live with HF, of which nearly half have preserved ejection fraction (HFpEF) (Chatterjee, 2002; Martos *et al*., 2007; Lanier *et al*., 2012; Go *et al*., 2013). As HF has predominantly been associated with reduced LV contractility and reduced ejection fraction, prevalence and incidence of HFpEF is difficult to estimate (Chatterjee, 2002; Hunt *et al*., 2009). To date, successful prevention and treatment of HFpEF presents a challenge due to the limited number of clinical trials (Hunt *et al*., 2009; Lanier *et al*., 2012). Although HFrEF and HFpEF can present with similar signs and symptoms (dyspnea, fatigue, edema), these two types of HF have different underlining pathophysiologic mechanisms (Borlaug & Redfield, 2011). Additionally, patients may have both forms of HF, which makes treatment more difficult.

Whereas various medications have been successfully used for patients with HFrEF, these same medications are not producing similar benefits in patients with HFpEF (Borlaug & Redfield, 2011), prompting the need for specific research to treat the underlying mechanism(s) that lead to the development of diastolic dysfunction and subsequent HFpEF. Oxidative stress occurs in diastolic dysfunction and HFpEF when there is an imbalance between ROS production and antioxidant defense, such as offered by CoQ_{10}. With existing studies exhibiting multifaceted benefits from ubiquinol supplementation, research is warranted to evaluate the potential of ubiquinol in the prevention and/or treatment of diastolic dysfunction and subsequent HFpEF.

CONCLUSIONS

Heart failure with preserved ejection fraction is an increasingly prevalent health problem and the current therapy does not reduce morbidity and mortality. This disease is a heterogeneous condition with variable pathophysiologic processes; however, a common feature in HFpEF is impaired mitochondrial energetics. One possible cause of mitochondria dysfunction is diminished ubiquinol, which is essential for ATP biosynthesis. Thus, supplementation of ubiquinol may be useful in enhanced mitochondrial energetics, resulting in improved myocardial function. Since patients with HFpEF have increased oxidative stress, it is important to add an antioxidant to their treatment regimen. One possible supplement for diastolic heart failure patients is ubiquinol. It is a potent antioxidant that has been shown to attenuate oxidative stress in myocardium.

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CONTRIBUTIONS

Literature Search: AB, QS, ART, JBH, JDP.
Manuscript Writing: AB, QS, ART, JBH, JDP.
Manuscript Revision: QS, ART, JBH, JDP

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