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The Modulating Effects of Cardiac Resynchronization Therapy on Myocardial Metabolism in Heart Failure

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Abstract

Heart failure (HF) is associated with changes in cardiac substrate utilization and energy metabolism, including a decline in high-energy phosphate content, mitochondrial dysfunction, and phosphotransfer enzyme deficiency. A shift toward glucose metabolism was noted in the end stage of HF in animals, although HF in humans may not be associated with a shift toward predominant glucose utilization. Deficiencies of micronutrients are well-established causes of cardiomyopathy. Correction of these deficits can improve heart function. The genes governing the energy metabolism were predominantly under-expressed in nonischemic cardiomyopathy and hypertrophic cardiomyopathy but were overexpressed in ischemic cardiomyopathy. Cardiac resynchronization therapy (CRT) has been proven to increase cardiac efficiency without increasing myocardial oxygen consumption. Altered myocardial metabolism is normalized by CRT to improve ventricular function.

Keywords

cardiac resynchronization therapy; heart failure; metabolism; metabolomics

Introduction

Heart failure (HF) is the consequence of advanced structural heart diseases. At the cellular level, HF is associated with changes in energy metabolic networks and substrate utilization.¹ Adenosine triphosphate (ATP) turnover in the failing myocardium may be reduced by as

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much as 30%.² The metabolic characteristics of a failing heart include high-energy phosphate and phosphotransfer enzyme deficiency, mitochondrial dysfunction, and increased myocardial consumption of glucose.^{3–5} Therefore, HF is associated with not only physiological alteration, including pressure and volume overload, but also with metabolic alteration manifested as gradual ATP decrease, generated by the myocardium.⁶ The metabolic changes, along with altered timing and coordination of cardiac contractions and especially in the ventricles, are thought to contribute to the development of cardiac failure.^{7,8}

Cardiac resynchronization therapy (CRT) is a nonpharmacological therapy by which simultaneous stimulation of both ventricles improves HF symptoms and ventricular function, and furthers overall survival.⁹ A recent study has documented that CRT normalizes myocardial metabolic alterations, suggesting a strong relation between cardiac contractility and the bioenergetic system.¹⁰ We highlight the novel metabolic features in the development of HF and the modulating effects of CRT on myocardial metabolism.

Metabolic Alterations in the Failing Heart

Carbohydrates and Lipids

In animals with left ventricular (LV) hypertrophy and HF, a relative switch toward increased glucose utilization has been shown. In the early stage of the canine rapid-pacing model of HF, substrate utilization was not altered. However, a shift toward glucose metabolism was noted in the end stage of HF.⁷ This shift in metabolism was attributed to reduced expression and activity of retinoid X receptor α , a receptor known to stimulate expression of medium-chain acyl-CoA dehydrogenase and enzymes involved in free fatty acid (FFA) oxidation.

Other complex mechanisms may be responsible for the shift to this fetal phenotype. Increased adenosine monophosphate (AMP) and AMP kinase activity has been reported in hypertrophied rat hearts undergoing transition to HF.¹¹ Increased AMP kinase activity increases glucose uptake through glucose transporter 1 and increases glycolysis through phosphorylation of 6-phosphofructo-2-kinase.¹² Long-term activation of AMP kinase also decreases FFA utilization through decreased expression of carnitine palmitoyl transferase 1 and medium-chain acyl-CoA dehydrogenase enzymes.¹³

Still uncertain is whether the shift toward glucose metabolism in experimental models of HF is adaptive or maladaptive, and human HF may not be associated with a shift toward predominant glucose utilization. Taylor et al.¹⁴ found that myocardial FFA and glucose use in HF can be assessed quantitatively through positron emission tomography (PET) with radiotracer, demonstrating increased myocardial FFA uptake and reduced glucose uptake in human HF. Uriel et al.¹⁵ found that plasma norepinephrine correlated with FFA levels in HF patients and contributed to insulin resistance. Furthermore, Tucci et al. and Xiong et al.^{16,17} found that primary cardiomyopathy and HF were associated with mutations in the human very-long-chain acyl-CoA dehydrogenase gene, which catalyzes the first step in the FFA β -oxidation. Tuunanen et al.¹⁸ suggested that inhibition of FFA metabolism with trimetazidine, the selective inhibitor of mitochondrial long-chain 3-ketoacyl CoA thiolase, has beneficial effects on cardiac performance, exercise capacity, and clinical symptoms in patients with

chronic HF. However, acute reduction of FFA uptake and oxidation may not be beneficial in HF.¹⁹

Micronutrients

Besides glucose and FFA, which are used as fuel by the myocardium, various small molecules serve as important cofactors for energy transfer and production, and for cardiac output and function.⁵ These substances, including coenzyme Q10, L-carnitine, thiamine, and amino acids, are defined as *micronutrients*. Deficiencies of L-carnitine, thiamine, and taurine alone are well-established causes of cardiomyopathy and HF.^{20–23}

Micronutrients are auxiliary, but essential, for the myocardium to utilize energy substrate, and thereby maintain normal structure and function. Thus, correction of these deficits can improve cardiac function.^{24–26} Sequentially, micronutrient supplementation for HF improves the energy utilization efficiency in the myocardium and restores cell function. Ayer et al. and DiNicolantonio et al. found that when HF patients received megadoses of coenzyme Q10, their LV ejection fraction and New York Heart Association (NYHA) class improved significantly.^{23,27} The improvement of LV function is correlated with increased plasma coenzyme Q10 levels.

Metabolic Gene Expression in HF

Kittleson et al.²⁸ analyzed myocardium samples from patients who underwent LV assist device placement or cardiac transplantation, demonstrating differential gene expression between ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NICM). They used microarray techniques to identify 257 genes in NICM and 72 genes in ICM that were differentially expressed compared with nonfailing hearts. Those genes uniquely expressed in NICM were frequently associated with lipid metabolism. Only 41 genes involving cell growth and signal transduction were shared between NICM and ICM.

Colak et al.²⁹ used the same methods to analyze the myocardial tissue of patients with dilated cardiomyopathy, finding that genes involved in energy metabolic processes, such as the citric acid cycle and ATP synthesis, were upregulated. This heightened level of metabolic activity may be a compensatory mechanism in this disease process. When the heart adapts to chronic pathophysiological conditions, such as ischemia or pressure or volume overload, changes in metabolic enzymes are also induced at a transcriptional or posttranslational level, or both, including the induction of regulating genes and a switch in substrate. In a mice experimental model, Oka et al.³⁰ found that the cardiac peroxisome proliferator-activated receptor- α regulates the expression of several key enzymes involved in cardiac mitochondrial fatty acid utilization, thus upregulating FFA uptake, transport into mitochondria, and β -oxidation. The increased FFA utilization causes a decrease in glucose metabolism. However, hypoxia-inducible transcription factor 1- α , as a transcription regulator, upregulates the glucose pathway through induction of glucose transporter 1 and glycolytic enzymes, such as aldolase A, phosphopyruvate hydratase, lactate dehydrogenase A, and 6-phosphofructokinase, which increases anaerobic ATP synthesis, as adaptive responses to hypoxia.³¹

Effects of CRT on Myocardial Metabolism

Oxidative Metabolism and Myocardial Efficiency

Nelson et al.³² found that CRT enhanced the cardiac systolic function with decreasing myocardial oxygen consumption (MVO_2) accompanying unchanged coronary arterial blood flow velocity. They found that biventricular pacing increased LV dP/dt_{max} by 43% during CRT, while MVO_2 decreased by 8%. Their initiative study showed that CRT acutely enhances systolic function while it modestly lowers energy cost in patients who have dilated cardiomyopathy with left bundle branch block (LBBB).

In a study by Christenson et al.,³³ patients with NYHA class III HF were followed for 6 months after CRT implant. Myocardial oxidative metabolism and efficiency were calculated after 1 hour of atrial pacing with intrinsic atrioventricular conduction, simultaneous CRT, and sequential CRT, using ^{11}C -acetate PET and echocardiography. They concluded that CRT increased LV stroke volume index without increasing myocardial oxidative metabolism, resulting in improved myocardial efficiency. The investigators found additional potential of improvements in LV work, oxidative metabolism, and efficiency from simultaneous to sequential CRT, but the improvements were not significant. Yet, Brandao et al.³⁴ observed that despite the lack of increase in LV ejection fraction after CRT, some patients had an increase in LV regional wall uptake of technetium Tc 99m hexakis-2-methoxy isobutyl isonitrile (MIBI), an indicator of improved cellular perfusion and mitochondrial function. These favorable effects may explain why CRT improves functional class even for patients who do not show an increase in LV ejection fraction and ventricular reverse remodeling.

Patients with LV systolic dysfunction and dilatation frequently have LBBB, which is associated with delayed contraction of the lateral LV wall. The oxidative metabolism in the septal wall has been found to be lower than that in the lateral wall in patients with LBBB and HF.³⁵ After CRT, the oxidative metabolism increases in the septum by 22–45%.^{33,35–37} The improved septallateral ratio of the oxidative metabolism, accompanied by electrical and mechanical resynchrony, is supposed to be the sign of benefits from CRT. In addition, some studies focused on the performance of CRT during stress have found that CRT has beneficial effects on myocardial work and energetics at rest.

Braunschweig et al.³⁸ selected patients with sinus rhythm and successfully treated them with biventricular pacing for more than 1 year. They then halted CRT for 2 weeks. With the pacing on and off at resting conditions, the myocardial blood flow and MVO_2 were similar. However, the ability to increase the global MVO_2 during stress was impaired significantly with CRT cessation. The maladaptation of oxygen metabolism in response to stress when CRT is not administered reflects how CRT improves oxidative metabolic reserve in HF patients. Sundell et al.³⁹ also investigated HF patients with long-term biventricular pacing therapy with short (24-hour) cessation of CRT. At rest, the patients' LV stroke volume was significantly reduced, but LV oxidative metabolism was unchanged when CRT was off, implying a significant deterioration of myocardial efficiency. During dobutamine stress, stroke volume and oxidative metabolism were not changed, but myocardial efficiency and metabolic reserve tended to decrease when CRT was off. The investigators suggested that CRT effect on myocardial efficiency seemed to be smaller during stress than at rest.

Glucose Metabolism

The findings in glucose uptake after CRT have been consistent. The regional heterogeneity in glucose uptake that is typical in patients with HF and LBBB is nearly normalized with CRT. Investigators have observed that septal glucose uptake becomes increased and the global uptake becomes more homogeneous by using both cardiac fluorodeoxyglucose (FDG)-PET in a basal condition and 3 weeks of CRT.^{10,40}

Inoue et al.⁴¹ investigated the prognosis in patients undergoing CRT with use of combined fludeoxyglucose F 18–FDG-PET and MIBI-single-photon emission computed tomography (SPECT). The simultaneous evaluation with FDG-PET and MIBI-SPECT provides information on the patterns of myocardial blood flow and metabolism, such as match, mismatch, and reversed mismatch. In this small group study, all patients had LBBB. Such patients are known to show a reverse mismatch pattern in the septum⁴²—that is, less glucose metabolism compared with perfusion (MIBI uptake > FDG uptake).

LBBB causes intraventricular asynchrony with a delayed LV lateral wall contraction than the septum. This intraventricular asynchrony results in a reduction of septal workload. Further, the survival benefit after CRT is positively associated with the severity of reverse mismatch pattern, suggesting that the degree of reverse mismatch pattern in the septum is parallel to the extent of intraventricular asynchrony. Correction of intraventricular dyssynchrony with CRT in patients who have LBBB improves septal glucose metabolism and rebalances LV global workload and energy utilization. The enhanced myocardial efficiency improves myocardial remodeling and contractile function, which are translated to improvement in HF symptoms, reduced hospitalization for worsening HF, and improved survival (Fig. 1).

Perspectives

As in the aforementioned studies, PET or SPECT imaging enables noninvasive evaluation of regional myocardial perfusion and intracellular metabolism pathways. Quantitative metabolic parameters can be derived on the basis of the distribution and kinetics of the radiolabeled tracers. However, the conclusion of metabolic alteration was inferred indirectly through use of these imaging methods. The improvement of the uptake of labeled substrate is not equal to the utilization of energetic substrate in the myocardium.

Metabolomics is one of the most rapidly growing areas of contemporary science. *Metabolome* is defined as the total complement of small-molecule metabolites found in or produced by an organism. The importance of measuring small-molecule metabolites has become increasingly clear: the process of diseases and assessment of therapies can be actually and directly correlated with alteration in metabolite concentrations.

Metabolomics studies related to HF have centered on the search for biomarkers of disease progress.^{43–46} In one previous study, the serum metabolome was studied in a group of patients with HF and a reduced LV ejection fraction.⁴⁷ Among the many metabolites that were altered, 2-oxoglutarate and pseudouridine were examined in detail. Studying these two metabolites provided a more sensitive and more specific diagnosis of HF than monitoring brain natriuretic peptide levels. Thus, metabolomics is expected to become more widely

applied to cardiovascular research, especially the effects of CRT on the metabolomic profile in advanced HF.

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Figure 1.

Cardiac resynchronization therapy: getting out of the vicious circle of heart failure. Cardiac remodeling accompanied with conduction abnormalities and dyssynchrony in HF results in poorly coordinated, inefficient contractions. This precipitates metabolic heterogeneity and energetic inefficiency associated with elevated levels of plasma and myocardial free fatty acids (FFAs), which negatively impact on the glycolytic adenosine triphosphate (ATP)/energy transfer mechanism, perpetuating energetic imbalances and electrical instability. Cardiac resynchronization therapy (CRT) results in synchronized efficient contractions and synchronized metabolic pacing, and $\text{Ca}^{2+}/\text{Mg}^{2+}$ signaling coordinates ATP/energy-producing and consuming pathways. These effects improve substrate delivery, reduce metabolic heterogeneity, and improve glycolytic/mitochondrial metabolism. Such functional and metabolic synchronization reverses structural and energetic remodeling, resulting in improvement of gene expression, mitochondrial proteome and functions, cardiac peak oxygen consumption, and metabolome. The major outcomes of the reversal of electrical/metabolic remodeling by CRT are improved cardiac output, improved quality of life, reduced morbidity, and improved survival.