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REVIEW ARTICLE—JSNC AWARD

Analysis of Cardiac Metabolic Remodeling in Heart Failure Using Nuclear Medicine and Its Application: Japanese Society of Nuclear Cardiology Award

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Abstract

Heart failure is associated with a significant change in the energy metabolism of the heart. We aimed to elucidate the altered energetics during the progression of heart failure. We used radioactive metabolic tracers to assess the substrate uptake. In a rat model of heart failure, the glucose uptake increased significantly at the stage of left ventricular hypertrophy, whereas the uptake of fatty acids decreased at the stage of heart failure, with decreased energy reserve during the transition of cardiac hypertrophy to failure. Metabolic modulator which enhances glucose oxidation ameliorated the decrease in cardiac function. We also validated the close correlation with mitochondrial membrane potentials and ^{99m}technetium sestamibi (^{99m}Tc-MIBI) in vivo and at the organ level. The retention of ^{99m}Tc-MIBI signals was correlated with the severity of heart failure. Nuclear medicine is a powerful tool to understand the mechanism of cardiac remodeling in heart failure.
Keywords: Heart failure, Metabolic remodeling, Mitochondria
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Heart failure is associated with a significant change in the energy metabolism of the heart, and the altered energetics are hypothesized to play an important role in the progression of heart failure (1). The direct measurement of flux through various pathways of energy metabolism using radio-labeled substrates has served as a model system to elucidate the mechanism of energy metabolism in an organ and has significantly increased our knowledge of cardiac energy metabolism (2). Despite intense research efforts, the precise mechanism by which the alteration of cardiac energy metabolism is induced and causes progression of heart failure is not clear. One reason for this is that current knowledge is based on studies analyzing different parameters of metabolism using different animal models or patients with different clinical backgrounds (3). Thus, we simultaneously analyzed cardiac function, substrate uptake, cardiac energy reserve, gene and protein expression, as well as amounts of metabolites using metabolomics, in a rat model of heart failure that shows a distinct transition from compensated left ventricular hypertrophy to heart failure.

Comprehensive analysis of the transition of cardiac hypertrophy to heart failure

Dahl salt-sensitive rats fed a high-salt diet developed hypertension and left ventricular hypertrophy at 11 weeks of age and congestive heart failure at 17–19 weeks (4, 5). At around 17 weeks of age, they showed signs of heart failure and decreased systolic function (Figure 1). Dahl rats fed a low-salt diet were used as age-matched controls. The phosphocreatine to adenosine triphosphate (ATP) ratio started to decrease at the left ventricular hypertrophy stage, and significantly decreased at the heart failure stage (Figure 1) (3). Glucose uptake increased and fatty acid uptake was preserved at the left ventricular hypertrophy stage, confirmed by auto-radiography (6). Glucose uptake further increased and fatty acid uptake decreased at the heart failure stage (Figure 1). The expression of genes related to glycolysis, fatty acid oxidation, and mitochondrial function was preserved at the left ventricular hypertrophy stage and decreased at the heart failure stage, associated with decreases in levels of transcriptional regulators consistent with decreased mitochondrial-related gene and

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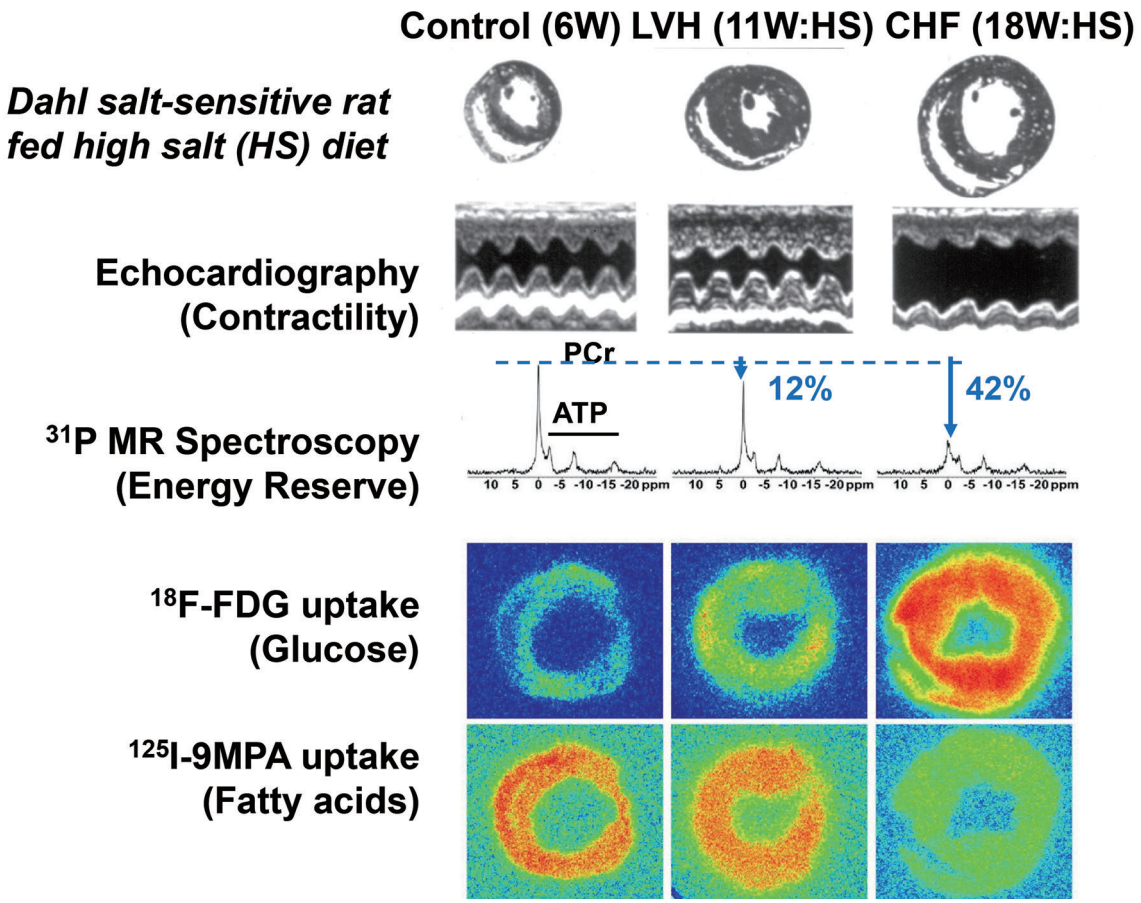

Figure 1　Analysis of cardiac energy metabolism in a rat model showing the transition from LVH to CHF.
Top panels: Representative images of echocardiography. Second panels: PCr/ATP determined by in vivo magnetic resonance spectroscopy. Third panels: Representative images of myocardial uptake of a glucose tracer, ^{18}F-FDG. Uptake of ^{18}F-FDG increased by 1.4 fold in LVH rats and 2.4 fold in HF rats compared to control rats. Fourth panels: Representative images of myocardial uptake of a fatty acid analogue, ^{125}I-9MPA. Uptake of ^{125}I-9MPA did not change in LVH rats and decreased by 36% in HF rats. ATP: adenosine triphosphate, CHF: congestive heart failure, ^{18}F-FDG: ^{18}F-fuorodeoxyglucose, HF: heart failure, HS: high salt, ^{125}I-9MPA: ^{125}I-15-(p-iodophenyl)-9-R, S-methylpentadecanoic acid, LVH: left ventricular hypertrophy, MR: magnetic resonance, PCr: phosphocreatine.

protein expression (3). To test whether enhanced glucose metabolism is a protective mechanism in heart failure, we administered Dahl rats with dichloroacetate, which activates pyruvate dehydrogenase and carbohydrate oxidation. Dichloroacetate preserved contractile function and improved the survival of the rats. Through metabolome analysis, a pathway highlighted in the study of Dahl rats was the pentose phosphate pathway, which is contributes to maintaining reduced glutathione and redox homeostasis. Metabolic remodeling of the heart causes cardiac dysfunction and can be a new therapeutic target for heart failure, for example, glucose oxidation (3) and amino acid metabolism (7). Metabolic alteration from fatty acid to glucose in the failing heart is reportedly considered to be due to the fetal gene reactivation program (8). From the mechanistic viewpoints, the disruption of a sarcoglycan-sarcospan complex in vascular smooth muscle cell disturbs vascular function, which in turn initiates the development of cardiomyopathy and exacerbate myocardial ischemia due to intra-myocardial microvascular dysfunction (9, 10). In addition, pressure overload by transverse aortic constriction induces hypoxia-inducible factor-1 and angiogenesis (11). Sustained pressure overload inhibits the activity of hypoxia-inducible factor-1 through accumulation of p53 (11); however, the accumulation of hypoxia-inducible factor-1 and p53 was not observed in our Dahl rat model (3). Collectively, these mechanisms may be associated with metabolic alteration and mitochondrial dysfunction in the failing myocardium in each pathophysiological context. In clinical settings, ^{18}F-fluorodeoxyglucose is possible to differentiate ischemic and infarcted myocardium (12) or to visualize the granulomatous region of sarcoidosis (13) on the basis of the presence of altered glucose metabolism.

Metabolic remodeling in the heart failure occurs not only in the heart, but also in the whole body (5, 14). Analysis of radioactive metabolic tracers revealed that the liver incorporates greater amounts of glucose in rats with heart failure. In conjunction with other analyses, the paradoxical production of triglyceride synthesis is also observed and is associated with a

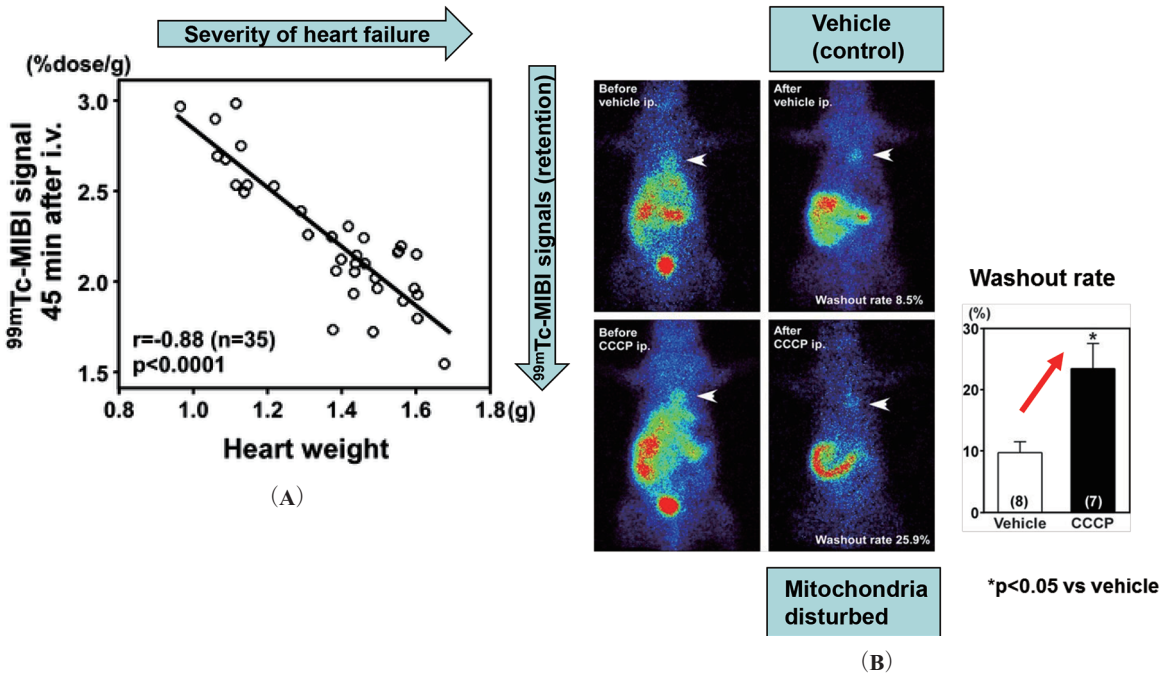

Figure 2 ^{99m}Tc-MIBI signals and the heart. (A) Correlation between ^{99m}Tc-MIBI signals and heart weight. ^{99m}Tc-MIBI signal per gram of heart tissue was inversely correlated with heart weight. (B) Representative in vivo images of ^{99m}Tc-MIBI distribution. Myocardial retention of ^{99m}Tc-MIBI was markedly decreased after the CCCP injection (lower panels) compared to vehicle-administered rats (upper panels). White arrowheads indicate hearts. Analysis of in vivo images showed that the ^{99m}Tc-MIBI washout rate was significantly increased in CCCP rats. CCCP; carbonyl cyanide m-chlorophenylhydrazone, ^{99m}Tc-MIBI: Technetium-99m sestamibi, WR, washout rate. All bars indicate means and SEMs. *P<0.05 vs vehicle-administered rats.

proinflammatory response in liver (14). Using radioactive metabolic tracers, we also found that cardiac-specific overexpression of the sirtuin gene, which is associated with longevity, and phosphoglycerate mutase, a glycolytic enzyme, causes cardiac dysfunction with altered mitochondrial morphology (15) or reduced anti-stress resistance in mice (16). These studies illustrate the link between metabolism, aging (15, 17, 18), and anti-stress resistance in the heart.

Mitochondrial dysfunction in heart failure

The mitochondria have a central role in the production of ATP in cells. Many methods have been used to assess mitochondrial function using isolated mitochondria, intact cells, or in situ techniques. However, little is known based on in vivo studies or at the organ level. ^{99m}Technetium sestamibi (^{99m}Tc-MIBI), a lipophilic cation, is rapidly incorporated into myocardial cells by diffusion and mainly localizes to the mitochondria. We analyzed ^{99m}Tc-MIBI signals in a perfused heart, excised heart tissue, and in vivo using Sprague-Dawley rats and carbonyl cyanide m-chlorophenylhydrazone (CCCP), a mitochondrial uncoupler known to reduce the mitochondrial membrane potential. ^{99m}Tc-MIBI signals decrease in rat hearts administered CCCP (Figure 2A) (19), and the ATP content, as measured by ^{31}P magnetic resonance spectroscopy, decreases simultaneously. The ^{99m}Tc-MIBI signal per heart tissue weight is inversely correlated with the severity of heart failure in the Dahl rat model (19). On in vivo imaging, CCCP increases the clearance of ^{99m}Tc-MIBI (Figure 2B), showing that the washout rate is increased in rats administered CCCP (20). To gain insight into the mechanisms underlying mitochondrial dysfunction and exercise intolerance in heart failure, we analyzed ^{99m}Tc-MIBI washout of the heart and leg muscles along with other clinical and cardiopulmonary exercise parameters. ^{99m}Tc-MIBI washout of the heart is correlated with brain natriuretic peptide levels and the washout rate of the leg muscle (21). Peak oxygen consumption was negatively correlated with the ^{99m}Tc-MIBI washout of the leg muscles (21). These studies indicated the potential linkage between mitochondrial function of the heart and leg muscles and brain natriuretic peptide levels in patients with heart failure, suggesting the mechanism of the beneficial effect of exercise in patients with heart failure. From the clinical viewpoints, the effects of inhibitors of sodium glucose cotransporter 2 highlighted the importance of cardiac and systemic metabolic remodeling in heart failure and diabetes mellitus (22).

Conclusions

Nuclear medicine has been and will continue to be a powerful tool to understand the metabolic remodeling of the heart both in clinical and basic contexts.

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Conflicts of interest

None.

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