Molecular Imaging of the Failing Heart: Assessment of Cardiac Sympathetic Nerve and Mitochondrial Function

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Abstract

Patients with heart failure have a high morbidity and mortality despite the advancement of recent heart failure treatment. It is important to evaluate the mechanism of the failing myocardium for decision making appropriate managements or the prediction of prognosis in patients with heart failure. Myocardium mainly utilizes fatty acid or glucose as the energy substrate of oxidative regeneration of ATP in the mitochondria. Intracellular calcium handling, that needs an amount of ATPs in several processes, induces myocardial contraction and relaxation by the sliding of the actin-myosin filament. Moreover, beta adrenal-stimulus also regulates intracellular calcium handling. In the failing myocardium, these components related to the myocardial work are variedly impaired, by various etiologies, including ischemia, inflammation, oxidative stress, metabolic or structural disorder, mechanical stress, or various other factors, and could become the imaging targets. In this review article, we focus on the clinical usefulness of 2 radionuclide imaging in evaluating sympathetic nerve function using myocardial 123I-MIBG SPECT and mitochondrial function using myocardial 99mTc-sestamibi SPECT in the failing heart. We summarize the relationship between each scintigraphic finding derived from the above mentioned tracers and myocardial functional properties of force frequency relations, the molecular mechanism of mitochondrial function, calcium handling, or beta-adrenal signaling in patient with cardiomyopathy.

Keywords:
Mitochondrial function, calcium handling, or beta-adrenal signaling in patient with cardiomyopathy.

Introduction

Patients with heart failure have a high morbidity and mortality despite the recent advancement of heart failure treatment. The number of patients is markedly increasing, and five-year mortality still remains approximately 50% [1]. The condition of heart failure is defined as the decompensation of the hemodynamics with insufficient blood demand to peripheral tissues, not only due to low cardiac output caused by reduced myocardial contraction, but also due to the impairment of myocardial stiffness, increased vessel resistance, or systemic fluid unbalance. Even if cardiac function is preserved at rest, the impairment of myocardial relaxation in left ventricular hypertrophy [2], or the reduced myocardial functional reserve in myocardial contraction and relaxation at physical or pharmacological stress [3,4] could cause heart failure. Accordingly, it is important to evaluate in detail the myocardial property of the failing heart with reduced cardiac functional reserve.

The pathogenesis of the failing heart is fundamentally classified into 2 types as myocardial ischemia and non-ischemia. Several reports showed the clinical relevance of assessing of myocardial ischemia in consideration of indication of revascularization for the favorable prognosis in patients with ischemic heart disease using myocardial perfusion single-photon emission computed tomography (SPECT) imaging [5] or using a coronary pressure wire [6,7].

Non ischemic pathogenesis of the failing heart is varied and complex, such as genetically metabolic or protein production disorder, pressure or volume overload caused by hypertension or vuvlar disease, microvascular dysfunction, drug-induced injury, inflammation observed in cardiac sarcoidosis or myocarditis, and so on. It is important to evaluate the mechanism and clinical condition of the failing heart for decision making appropriate treatments or the prediction of prognosis in patients with heart failure using non-invasive imaging, such as echocardiography, nuclear cardiology imaging, cardiac magnetic resonance image (MRI), or computed tomography (CT) [8-10].

In nuclear imaging of the failing heart, the impaired site of the pathogenesis of the failing heart related to several process of myocardial ischemia, inflammation, or fibrosis could be visualized with radionuclide imaging. Myocardium mainly utilizes fatty acid or glucose as the energy source with oxygen in the aerobic metabolism, and each of them is targeted as 18F-fludeoxyglucose (FDG)-postin emission tomography (PET), 123I-beta-methyl-p-iodophenylpentadecanoic acid (BMIPP), or 18C-Acetate PET [11]. Specifically, 123I-BMIPP imaging [12,13] and 18F-FDG-PET are commonly used for the evaluation of the failing heart in clinical practice.

Abbreviations

MIBG: Metaiodobenzilguanidine
DCM: Dilated Cardiomyopathy
HCM: Hypertrophic Cardiomyopathy

ATP: Adenosine Triphosphate
SPECT: Single-Photon Emission Computed Tomography
PET: Positron Emission Tomography


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setting and are recommended modalities in the guidelines [14]. Fatty acid or glucose is utilized as the energy substrate of oxidative regeneration of adenosine triphosphate (ATP) in the mitochondria, and the mitochondrial function is visualized with 99mTc-sestamibi [15,16], as described in detail later. Moreover, intracellular calcium handling, that needs an amount of ATPs in several processes, induces myocardial contraction and relaxation by the sliding of actin-myosin filament. Beta adrenal-stimulus by sympathetic nerve in the myocardium also regulates the intracellular calcium handling, and the myocardial sympathetic nerve function is imaged with 123I-metaiodobenzylguanidine (123I-MIBG). In addition, the inflammation observed in cardiac sarcoidosis [17] or myocarditis could be identified with 18F-FDG-PET, and the images of myocardial fibrosis [18] or amyloid are also investigated. Also, intramyocardial microvascular dysfunction could be seen in patients with hypertrophic cardiomyopathy (HCM) [19,20], those with diabetic cardiomyopathy, or those with chronic kidney disease [21,22] using myocardial rubidium (82Rb) or ammonia (15N-NH3) PET imaging.

This review article focuses on the clinical usefulness of 2 radionuclide imaging in evaluating myocardial mitochondrial function using myocardial 99mTc-sestamibi and sympathetic nerve function using myocardial 123I-MIBG in patients with cardiomyopathy. Moreover, we examine the relationship between each of the imaging parameters and myocardial functional properties of force frequency relations, the molecular mechanism of mitochondrial function, calcium handling, or beta-adrenal signaling.

**Sympathetic Nerve Functional Imaging with 123I-MIBG**

Myocardial imaging with 123I-MIBG, the analogue of norepinephrine (NE), could visualize innervations and activity of the adrenal sympathetic nervous system, and is widely used for the evaluation of patients with heart failure [23,24]. It is well known that the abnormality of sympathetic nervous system, as increased nervous activity or denervation, are seen in heart failure patients, and imaged with 123I-MIBG [25]. Several reports showed the clinical usefulness of 123I-MIBG for the predictor of major cardiac events, such as heart failure hospitalization or cardiac death [26-29], discharge of implantable cardioverter defibrillator [30], or evaluation of the effectiveness of beta-blockade [31-35], renin-angiotensin-aldosterone system inhibitor [36-38], and niconradil [39, 40] in patients with heart failure due to various pathogenesis, such as cardiomyopathy or ischemic heart disease. Recently, the standardization of the parameters, heart to mediastinum ration (H/M) or washout rate, became possible by the correction of the difference of a collimator-parameters, heart to mediastinum ration (H/M) or washout rate, that needs an amount of ATPs in several processes, became possible by the correction of the difference of a collimator-scinticamera system using the calibration phantom [41,42]. Thus, a multi-center study named ADMIRE-HF trial was conducted [43], and meta analysis of Japanese single cohort was also performed [44]. 123I-MIBG SPECT is accepted as class I on the guideline of the clinical use of nuclear medicine for patients with heart failure according to the Japanese Circulation Society [45].

On the other hand, reduced myocardial functional reserve during a trial pacing tachycardia or during dobutamine stress test is reportedly caused by the impairment of intracellular calcium handling, especially of SERCA2 or phospholamban [46-48] in the failing heart; and that is related to the poor prognosis [4,49]. However, the relationship between calcium handling and findings of non-invasive imaging has not yet been investigated.

- We therefore investigated the relationship between parameters of myocardial 123I-MIBG SPECT, myocardial functional reserve during atrial pacing stress or dobutamine stress, and mRNA gene expression of the protein related to calcium handling or beta-adrenal signaling in myocardial tissue in patients with idiopathic dilated cardiomyopathy (DCM) and HCM.

At first, we reported that patients with reduced delayed H/M showed an impairment in myocardial functional reserve with reduced mRNA expressions of sarcoplasmic reticulum calcium ATPase (SERCA2a) and phospholamban during atrial pacing tachycardia in 24 DCM patients [50].

Next, we demonstrated significant correlations between washout rate or delayed H/M and myocardial functional reserve in DCM patients (Figure 1) [51,52]. Moreover, these parameters also associated with mRNA expressions of the proteins related to calcium handling or beta-adrenal signaling.

We also demonstrated that 123I-MIBG parameters are associated with impaired myocardial functional reserve during atrial pacing tachycardia in 30 HCM patients [53].

**Mitochondrial Functional Imaging with 99mTc-Sestamibi**

Myocardial mitochondria produce ATP as a myocardial energy source [54]. Intra-mitochondria have a strong negative membrane potential of -161±7 mV [55]. When cardiomyocytes are impaired by myocardial ischemia or other causes, the mitochondrial membrane potential is increasing [56].

99mTc-sestamibi, which is generally used as the tracer of myocardial perfusion imaging, is a mono-positive ion, and usually retained within the mitochondria by the strong negative membrane potential [57]. However, when mitochondria is impaired, the mitochondrial membrane potential increases, and subsequently 99mTc-sestamibi is washed out [58].

It is reported that mitochondria in large clusters varied in size and shape with few myofibrils in cytoplasm of extracted myocardial tissue of DCM patients [59]. Also, it is reported that mitochondrial damages were seen in several other heart diseases [54].

In experimental studies, increased washout of 99mTc-sestamibi was demonstrated in the pathological situation with mitochondrial injury as a model of myocardial ischemia and reperfusion[60], of hypertensive heart failure [61], and of pharmacological mitochondrial injury [62].

And also, several clinical investigations have demonstrated that washout of 99mTc-sestamibi is observed in patients with myocardial infarction after reperfusion [63,64], those with severe ischemia with triple vessel disease [65], those with non-ischemic cardiomyopathy[15, 66,67], those with mitochondrial cardiomyopathy [68], and those with post-chemotherapy cardiomyopathy [69].

We similarly investigated the relationship between the washout of 99mTc-sestamibi and the myocardial functional reserve of force frequency relation in patients with non-ischemic cardiomyopathy.

We demonstrated that washout rate of 99mTc-sestamibi was associated with myocardial functional reserve during dobutamine

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stress, mitochondrial morphological, and functional abnormalities in 20 DCM patients (Figure 2) [70]. DCM patients with increased washout of $^{99m}$Tc-sestamibi showed reduced mRNA expressions of the proteins related to the mitochondrial electron transport chain. Significant correlations were observed between washout rate of $^{99m}$Tc-sestamibi and mitochondrial morphological abnormalities, as shown in the abnormal mitochondrial shape and size, degeneration of the cristae formation, and the presence of glycogen positive area which represent impairments in glucose utilization.

In 30 HCM patients, increased washout of $^{99m}$Tc-sestamibi was also related with impaired force frequency relations during atrial pacing stress, and with mitochondrial functional damage of the protein related to electron transport, morphological abnormality of mitochondria as shown in disorganization or variation in size and increased number of mitochondria (Figure 3) [71,72].

Clinal Significance of Each Imaging in the Failing Heart

Myocardial mitochondria produce about 30 kg/day of ATP to maintain myocardial function [54]. Myocardial contraction and relaxation are caused by sliding of actin and myosin filaments with intracellular calcium handling, which needs ATPs in several processes (Figure 4) [73]. When myocardial mitochondria are impaired, these processes do not work well, resulting in cardiac functional deterioration [74].

Beta-adrenal stimulus initiates and regulates the calcium handling process. The down-regulation of beta receptors in the failing myocardium impairs phosphorylation of phospholamban, reducing an influx of calcium into sarcoplasmic reticulum, eventually resulting in an impairment of cardiac function [75]. On the other hand, over-phosphorylation of ryanosine receptor of sarcoplasmic reticulum causes intracellular calcium overload, and also accelerates the reduction of cardiac function [76,77]. Carvedilol protects of SERCA2a [78], or metoprolol up-regulates the number of beta receptor [79], resulting in the amelioration of calcium handling, and subsequently restoring the cardiac function.

Consequently, it is clinically very important to figure out the perspective of the pathogenesis the failing heart, not only with regard to sympathetic nervous system or mitochondrial function but also calcium handling or beta-adrenal signaling using myocardial $^{99m}$Tc-sestamibi or $^{123I}$-MIBG imaging.

Conclusion

The myocardial imaging with $^{99m}$Tc-sestamibi and $^{123I}$-MIBG could visualize myocardial mitochondrial or sympathetic nerve function that is closely related to myocardial work in the molecular level. These radionuclide imaging contribute to make for a profound understanding of the essential mechanism of pathogenesis in the failing myocardium.

The nuclear imaging with several tracers could image several component related to the cardiac work, such as myocardial metabolism of glucose and fatty acid with oxygen, ATP production in mitochondria, sympathetic nerve function, in inflammation, or fibrosis. Assessments of the pathogenesis the failing myocardium using these tracers provide not only appropriate patient care and treatment but also prediction of prognosis in heart failure patients.

Competing Interests

The authors have no competing interests with the work presented in this manuscript.

Author Contributions

All the authors substantially contributed to the literature review, drafting the manuscript and approve the final version of the manuscript.

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References


the assessment of heart failure. World J Cardiol 2: 344-356.


the assessment of heart failure. World J Cardiol 2: 344-356.


the assessment of heart failure. World J Cardiol 2: 344-356.


the assessment of heart failure. World J Cardiol 2: 344-356.


the assessment of heart failure. World J Cardiol 2: 344-356.


