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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 ^{123}I-MIBG SPECT and mitochondrial function using myocardial ^{99m}Tc-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.

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Abbreviations

MIBG: Metaiodobenzilguanidine
DCM: Dilated Cardiomyopathy
HCM: Hypertrophic Cardiomyopathy
ATP: Adenosine Triphosphate
SPECT: Single-Photon Emission Computed Tomography
PET: Positron Emission Tomography

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 vulvular 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 ^{18}F-fludeoxyglucose (FDG)-positron emission tomography (PET), ^{123}I-beta-methyl-p-iodophenylpentadecanoic acid (BMIPP), or ^{11}C-Acetate PET [11]. Specifically, ^{123}I-BMIPP imaging [12,13] and ^{18}F-FDG-PET are commonly used for the evaluation of the failing heart in clinical

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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 ^{99m}Tc-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 ^{123}I-metaiodobenzil-guanidine (^{123}I-MIBG). In addition, the inflammation observed in cardiac sarcoidosis [17] or myocarditis could be identified with ^{18}F-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 (^{82}Rb) or ammonia (^{13}N-NH_3) PET imaging.

This review article focuses on the clinical usefulness of 2 radionuclide imaging in evaluating myocardial mitochondrial function using myocardial ^{99m}Tc-sestamibi and sympathetic nerve function using myocardial ^{123}I-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 ^{123}I-MIBG

Myocardial imaging with ^{123}I-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 ^{123}I-MIBG [25]. Several reports showed the clinical usefulness of ^{123}I-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 nicorandil [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-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]. ^{123}I-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 ^{123}I-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 ^{123}I-MIBG parameters are associated with impaired myocardial functional reserve during atrial pacing tachycardia in 30 HCM patients [53].

Mitochondrial Functional Imaging with ^{99m}Tc-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].

^{99m}Tc-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 ^{99m}Tc-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 ^{99m}Tc-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 ^{99m}Tc-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 ^{99m}Tc-sestamibi and the myocardial functional reserve of force frequency relation in patients with non-ischemic cardiomyopathy.

We demonstrated that washout rate of ^{99m}Tc-seatamibi was associated with myocardial functional reserve during dobutamine

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].

Clinical 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 ^{123}I-MIBG imaging.

Conclusion

The myocardial imaging with ^{99m}Tc-sestamibi and ^{123}I-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

1. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, et al. (2004) Trends in heart failure incidence and survival in a community-based population. JAMA 292: 344-350.
2. Hogg K, Swedberg K, McMurray J (2004) Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 43: 317-327.
3. Kitaoka H, Takata J, Yabe T, Hitomi N, Furuno T, et al. (1999) Low dose dobutamine stress echocardiography predicts the improvement of left ventricular systolic function in dilated cardiomyopathy. Heart 81: 523-527.
4. Scrutinio D, Napoli V, Passantino A, Ricci A, Lagioia R, et al. (2000) Low-dose dobutamine responsiveness in idiopathic dilated cardiomyopathy: relation to exercise capacity and clinical outcome. Eur Heart J 21: 927-934.
5. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS (2003) Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 107: 2900-2907.
6. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, et al. (2010) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 56: 177-184.
7. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, et al. (2014) Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 371: 1208-1217.
8. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, et al. (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 62: e147-239.
9. Carr JJ, Hendel RC, White RD, Patel MR, Wolk MJ, et al. (2013) 2013 appropriate utilization of cardiovascular imaging: a methodology for the development of joint criteria for the appropriate utilization of cardiovascular imaging by the American College of Cardiology Foundation and American College of Radiology. J Am Coll Radiol 10: 456-463.
10. White RD, Patel MR, Abbara S, Bluemke DA, Herfkens RJ, et al. (2013) 2013 ACCF/ACR/ASE/ASNC/SCCT/SCMR appropriate utilization of cardiovascular imaging in heart failure: an executive summary: a joint report of the ACR Appropriateness Criteria ® Committee and the ACCF Appropriate Use Criteria Task Force. J Am Coll Radiol 10: 493-500.
11. Naya M, Tamaki N2 (2014) Imaging of Myocardial Oxidative Metabolism in Heart Failure. Curr Cardiovasc Imaging Rep 7: 9244.
12. Ishida Y, Yasumura Y, Nagaya N, Fukuchi K, Komamura K, et al. (1999) Myocardial imaging with 123I-BMIPP in patients with congestive heart failure. Int J Card Imaging 15: 71-77.
13. Nishimura T (1999) beta-Methyl-p-(123I)-iodophenyl pentadecanoic acid single-photon emission computed tomography in cardiomyopathy. Int J Card Imaging 15: 41-48.

14. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, et al. (2009) ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol 53: 2201-2229.

15. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M (2007) A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. J Nucl Cardiol 14: 215-220.

16. Matsuo S, Nakajima K, Kinuya S (2010) Clinical use of nuclear cardiology in the assessment of heart failure. World J Cardiol 2: 344-356.

17. Schindler TH, Solnes L (2015) Role of PET/ CT for the Identification of Cardiac Sarcoid Disease. Ann Nucl Cardiol 1: 79-86.

18. van den Borne SW, Isobe S, Verjans JW, Petrov A, Lovhaug D, et al. (2008) Molecular imaging of interstitial alterations in remodeling myocardium after myocardial infarction. J Am Coll Cardiol 52: 2017-2028.

19. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, et al. (2003) Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med 349: 1027-1035.

20. Sciagrà R, Passeri A, Cipollini F, Castagnoli H, Olivotto I, et al. (2015) Validation of pixel-wise parametric mapping of myocardial blood flow with Â¹Â³NHâ‚ƒ PET in patients with hypertrophic cardiomyopathy. Eur J Nucl Med Mol Imaging 42: 1581-1588.

21. Kasama S, Toyama T, Iwasaki T, Sumino H, Kumakura H, et al. (2014) European Journal of Nuclear Medicine and Molecular Imaging, 41.

22. Fukushima K, Javadi MS, Higuchi T, Bravo PE, Chien D, et al. (2012) Impaired global myocardial flow dynamics despite normal left ventricular function and regional perfusion in chronic kidney disease: a quantitative analysis of clinical 82Rb PET/CT studies. J Nucl Med 53: 887-893.

23. Wieland DM, Wu J, Brown LE, Mangner TJ, Swanson DP, et al. (1980) Radiolabeled adrenergi neuron-blocking agents: adrenomedullary imaging with [131I]iodobenzylguanidine. J Nucl Med 21: 349-353.

24. Carrió I, Cowie MR, Yamazaki J, Udelson J, Camici PG (2010) Cardiac sympathetic imaging with mIBG in heart failure. JACC Cardiovasc Imaging 3: 92-100.

25. Jessup M, Brozena S (2003) Heart failure. N Engl J Med 348: 2007-2018.

26. Merlet P, Valette H, Dubois-Randé JL, Moyse D, Duboc D, et al. (1992) Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 33: 471-477.

27. Kasama S, Toyama T, Sumino H, Nakazawa M, Matsumoto N, et al. (2008) Prognostic value of serial cardiac 123I-MIBG imaging in patients with stabilized chronic heart failure and reduced left ventricular ejection fraction. J Nucl Med 49: 907-914.

28. Kasama S, Toyama T, Kurabayashi M (2015) Serial ^{123}I-metaiodobenzylguanidine imaging predicts the risk of sudden cardiac death in patients with chronic heart failure. Int J Cardiol 179: 82-83.

29. Merlet P, Benvenuti C, Moyse D, Pouillart F, Dubois-Randé JL, et al. (1999) Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. J Nucl Med 40: 917-923.

30. Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, et al. (2010) Cardiac sympathetic denervation assessed with 123-iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. J Am Coll Cardiol 55: 2769-2777.

31. Fukuoka S, Hayashida K, Hirose Y, Shimotsu Y, Ishida Y, et al. (1997) Use of iodine-123 metaiodobenzylguanidine myocardial imaging to predict the effectiveness of beta-blocker therapy in patients with dilated cardiomyopathy. Eur J Nucl Med 24: 523-529.

32. Kakuchi H, Sasaki T, Ishida Y, Komamura K, Miyatake K (1999) Clinical usefulness of 123I meta-iodobenzylguanidine imaging in predicting the effectiveness of beta blockers for patients with idiopathic dilated cardiomyopathy before and soon after treatment. Heart 81: 148-152.

33. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, et al. (2007) Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing carvedilol. Eur Heart J 28: 989-995.

34. Fujimoto S, Inoue A, Hisatake S, Yamashina S, Yamashina H, et al. (2004) Usefulness of 123I-metaiodobenzylguanidine myocardial scintigraphy for predicting the effectiveness of beta-blockers in patients with dilated cardiomyopathy from the standpoint of long-term prognosis. Eur J Nucl Med Mol Imaging 31: 1356-1361.

35. Cohen-Solal A, Rouzet F, Berdeaux A, Le Guludec D, Abergel E, et al. (2005) Effects of carvedilol on myocardial sympathetic innervation in patients with chronic heart failure. J Nucl Med 46: 1796-1803.

36. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, et al. (2003) Addition of valsartan to an angiotensin-converting enzyme inhibitor improves cardiac sympathetic nerve activity and left ventricular function in patients with congestive heart failure. J Nucl Med 44: 884-890.

37. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, et al. (2006) Comparative effects of valsartan and enalapril on cardiac sympathetic nerve activity and plasma brain natriuretic peptide in patients with congestive heart failure. Heart 92: 625-630.

38. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, et al. (2002) Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with congestive heart failure. J Nucl Med 43: 1279-1285.

39. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, et al. (2005) Effects of nicorandil on cardiac sympathetic nerve activity after reperfusion therapy in patients with first anterior acute myocardial infarction. Eur J Nucl Med Mol Imaging 32: 322-328.

40. Kasama S, Toyama T, Hatori T, Kumakura H, Takayama Y, et al. (2005) Comparative effects of nicorandil with isosorbide mononitrate on cardiac sympathetic nerve activity and left ventricular function in patients with ischemic cardiomyopathy. Am Heart J 150: 477.

41. Matsuo S, Nakajima K (2015) Assessment of caxardiac sympathetic nerve function using 123I-meta-iodobenzylguanidinescintigraphy: Technical aspects and standardization. Ann Nucl Cardiol 1: 27-34.

42. Nakajima K, Okuda K, Matsuo S, Yoshita M, Taki J, et al. (2012) Standardization of metaiodobenzylguanidine heart to mediastinum ratio using a calibration phantom: effects of correction on normal databases and a multicentre study. Eur J Nucl Med Mol Imaging 39: 113-119.

43. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, et al. (2010) Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 55: 2212-2221.

44. Nakata T, Nakajima K, Yamashina S, Yamada T, Momose M, et al. (2013) A pooled analysis of multicenter cohort studies of (123)I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. JACC Cardiovasc Imaging 6: 772-784.

45. JCS Joint Working Group (2012) Guidelines for clinical use of cardiac nuclear medicine (JCS 2010) -digest version -. Circ J 76: 761-767.

46. Feldman MD, Alderman JD, Aroesty JM, Royal HD, Ferguson JJ, et al. (1988) Depression of systolic and diastolic myocardial reserve during atrial pacing tachycardia in patients with dilated cardiomyopathy. J Clin Invest 82: 1661-1669.

47. Hasenfuss G, Holubarsch C, Hermann HP, Astheimer K, Pieske B, et al. (1994) Influence of the force-frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. Eur Heart J 15: 164-170.

48. Kim IS, Izawa H, Sobue T, Ishihara H, Somura F, et al. (2002) Prognostic value of mechanical efficiency in ambulatory patients with idiopathic dilated cardiomyopathy in sinus rhythm. J Am Coll Cardiol 39: 1264-1268.

49. Nagaoka H, Isobe N, Kubota S, Iizuka T, Imai S, et al(1997) Myocardial contractile reserve as prognostic determinant in patients with idiopathic dilated cardiomyopathy without overt heart failure. Chest 111: 344-350.

50. Ohshima S, Isobe S, Izawa H, Nanasato M, Ando A, et al. (2005) Cardiac sympathetic dysfunction correlates with abnormal myocardial contractile reserve in dilated cardiomyopathy patients. J Am Coll Cardiol 46: 2061-2068.

51. Kobayashi M, Izawa H, Cheng XW, Asano H, Hirashiki A, et al. (2008) Dobutamine stress testing as a diagnostic tool for evaluation of myocardial contractile reserve in asymptomatic or mildly symptomatic patients with dilated cardiomyopathy. JACC Cardiovasc Imaging 1: 718-726.

52. Ohshima S, Isobe S, Hayashi D, Abe S, Kato K, et al. (2013) Myocardial 123I-MIBG scintigraphy predicts an impairment in myocardial functional reserve during dobutamine stress in patients with idiopathic dilated cardiomyopathy. Eur J Nucl Med Mol Imaging 40: 262-270.

53. Isobe S, Izawa H, Iwase M, Nanasato M, Nonokawa M, et al. (2005) Cardiac 123I-MIBG reflects left ventricular functional reserve in patients with nonobstructive hypertrophic cardiomyopathy. J Nucl Med 46: 909-916.

54. Murray AJ, Edwards LM, Clarke K (2007) Mitochondria and heart failure. Curr Opin Clin Nutr Metab Care 10: 704-711.

55. Chen LB (1988) Mitochondrial membrane potential in living cells. Annu Rev Cell Biol 4: 155-181.

56. Konno N, Kako KJ (1991) Effects of hydrogen peroxide and hypochlorite on membrane potential of mitochondria in situ in rat heart cells. Can J Physiol Pharmacol 69: 1705-1712.

57. Carvalho PA, Chiu ML, Kronauge JF, Kawamura M, Jones AG, et al. (1992) Subcellular distribution and analysis of technetium-99m-MIBI in isolated perfused rat hearts. J Nucl Med 33: 1516-1522.

58. Chiu ML, Kronauge JF, Piwnica-Worms D (1990) Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis (2-methoxyisobutylisonitrile) technetium(I) in cultured mouse fibroblasts. J Nucl Med 31: 1646-1653.

59. Schaper J, Froede R, Hein S, Buck A, Hashizume H, et al. (1991) Impairment of the myocardial ultrastructure and changes of the cytoskeleton in dilated cardiomyopathy. Circulation 83: 504-514.

60. Li QS, Frank TL, Franceschi D, Wagner HN Jr, Becker LC (1988) Technetium-99m methoxyisobutyl isonitrile (RP30) for quantification of myocardial ischemia and reperfusion in dogs. J Nucl Med 29: 1539-1548.

61. Fukushima K, Momose M, Kondo C, Higuchi T, Kusakabe K, et al. (2010) Myocardial 99mTc-sestamibi extraction and washout in hypertensive heart failure using an isolated rat heart. Nucl Med Biol 37: 1005-1012.

62. Kawamoto A, Kato T, Shioi T, Okuda J, Kawashima T1, et al. (2015) Measurement of technetium-99m sestamibi signals in rats administered a mitochondrial uncoupler and in a rat model of heart failure. PLoS One 10: e0117091.

63. Takeishi Y, Sukekawa H, Fujiwara S, Ikeno E, Sasaki Y, et al. (1996) Reverse redistribution of technetium-99m-sestamibi following direct PTCA in acute myocardial infarction. J Nucl Med 37: 1289-1294.

64. Fujiwara S, Takeishi Y, Hirono O, Fukui A, Okuyama M, et al. (2001) Reverse redistribution of 99m Tc-sestamibi after direct percutaneous transluminal coronary angioplasty in acute myocardial infarction: relationship with wall motion and functional response to dobutamine stimulation. Nucl Med Commun 22: 1223-1230.

65. Du B, Li N, Li X, Li Y, Hsu B (2014) Myocardial washout rate of resting ??mTc-Sestamibi (MIBI) uptake to differentiate between normal perfusion and severe three-vessel coronary artery disease documented with invasive coronary angiography. Ann Nucl Med 28: 285-292.

66. Kumita S, Seino Y, Cho K, Nakajo H, Toba M, et al. (2002) Assessment of myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: comparison with normal control. Ann Nucl Med 16: 237-242.

67. Takehana K, Maeba H, Ueyama T, Iwasaka T (2011) Direct correlation between regional systolic function and regional washout rate of ??mTc-sestamibi in patients with idiopathic dilated cardiomyopathy. Nucl Med Commun 32: 1174-1178.

68. Ikawa M, Kawai Y, Arakawa K, Tsuchida T, Miyamori I, et al. (2007) Evaluation of respiratory chain failure in mitochondrial cardiomyopathy by assessments of 99mTc-MIBI washout and 123I-BMIPP/99mTc-MIBI mismatch. Mitochondrion 7: 164-170.

69. Carboni GP (2012) A novel clinical indicator using cardiac technetium-99m sestamibi kinetics for evaluating cardiotoxicity in cancer patients treated with multiagent chemotherapy. Am J Cardiovasc Dis 2: 293-300.

70. Hayashi D, Ohshima S, Isobe S, Cheng XW, Unno K, et al. (2013) Increased (99m)Tc-sestamibi washout reflects impaired myocardial contractile and relaxation reserve during dobutamine stress due to mitochondrial dysfunction in dilated cardiomyopathy patients. J Am Coll Cardiol 61: 2007-2017.

71. Unno K, Isobe S, Izawa H, Cheng XW, Kobayashi M, et al. (2009) Relation of functional and morphological changes in mitochondria to myocardial contractile and relaxation reserves in asymptomatic to mildly symptomatic patients with hypertrophic cardiomyopathy. Eur Heart J 30: 1853-1862.

72. Isobe S, Ohshima S, Unno K, Izawa H, Kato K, et al. (2010) Relation of 99mTc-sestamibi washout with myocardial properties in patients with hypertrophic cardiomyopathy. J Nucl Cardiol 17: 1082-1090.

73. Somura F, Izawa H, Iwase M, Takeichi Y, Ishiki R, et al. et al. (2001) Reduced myocardial sarcoplasmic reticulum Ca(2+)-ATPase mRNA expression and biphasic force-frequency relations in patients with hypertrophic cardiomyopathy. Circulation 104: 658-663.

74. Neubauer S (2007) The failing heart--an engine out of fuel. N Engl J Med 356: 1140-1151.

75. Kimura Y, Kurzydlowski K, Tada M, MacLennan DH (1997) Phospholamban inhibitory function is activated by depolymerization. J Biol Chem 272: 15061-15064.

76. Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D et al. (2000) PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. Cell 101: 365-376.

77. Yano M, Ono K, Ohkusa T, Suetsugu M, Kohno M, et al. (2000) Altered stoichiometry of FKBP12.6 versus ryanodine receptor as a cause of abnormal Ca(2+) leak through ryanodine receptor in heart failure. Circulation 102: 2131-2136.

78. Ribeiro RF Jr, Potratz FF, Pavan BM, Forechi L, Lima FL, et al. (2013) Carvedilol prevents ovariectomy-induced myocardial contractile dysfunction in female rat. PLoS One 8: e53226.

79. Yano M, Matsuzaki M (2001) [RyR-bound FKBP12.6 and the modulation]. Clin Calcium 11: 743-748.