

123I MIBG: Are There Any Additional Roles in Clinical Practice of Heart Failure?

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journal or publication title	Annals of Nuclear Cardiology
volume	1
number	1
page range	127-131
year	2015-01-01
URL	http://hdl.handle.net/2297/43646

doi: 10.17996/ANC.01.01.127

JSNC AWARD

¹²³I MIBG: Are There Any Additional Roles in Clinical Practice of Heart Failure?Kenichi Nakajima, MD, PhD¹⁾, Arnold F. Jacobson, MD, PhD²⁾

Received: July 4, 2015/Revised manuscript received: July 16, 2015/Accepted: July 17, 2015

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Abstract

Since the advent of ¹²³I-meta-iodobenzylguanidine (MIBG) in 1990s, it has been widely used in clinical practice in Japan. Based on the wide range of clinical applications, ¹²³I MIBG is now incorporated in Japanese Circulation Society's guidelines of nuclear cardiology. The major role of ¹²³I MIBG has been in determination of severity and prognostic evaluation of heart failure. In addition, assessment of the treatment by various types of medications has been the second major role of ¹²³I MIBG imaging. Compared with the conventional clinical parameters of heart failure, additive values of ¹²³I MIBG depend on how it reflects the patient condition more accurately, and how it relates to improvement in the patient outcome. ¹²³I MIBG is also now available for cardiac imaging in the USA and Europe. Unified methodology and further studies focusing on clinical decision-making are the next required steps to document MIBG utility.

Keywords: ¹²³I meta-iodobenzylguanidine (MIBG), Chronic heart failure, Decision making, Prognosis, therapeutic intervention

Ann Nucl Cardiol 2015 ; 1 (1) : 127-131

¹²³I metaiodobenzylguanidine (MIBG) was officially approved for clinical use by Japanese Ministry of Health and Welfare in Japan in 1992, and has been commercially available for 23 years. ¹²³I MIBG (MyoMIBG, FUJIFILM RI Pharma, Co. Ltd, Tokyo, Japan) is included in Japanese Circulation Society (JCS) clinical guidelines of nuclear cardiology (1), and has been one of the well-recognized radiopharmaceuticals. Clinical use of ¹²³I MIBG is much more common in Japan than Europe, where the product has been commercially available for a similar length of time. In contrast, ¹²³I MIBG was only approved by Food and Drug Administration in the USA for use in cardiology in 2013.

The broad clinical approval of ¹²³I MIBG in Japan, encompassing cardiac diseases as a whole, has encouraged its use in a wide variety of cardiac conditions. The applications have included assessment of denervated

but viable myocardium after acute myocardial infarction, primary and secondary cardiomyopathies, and serious arrhythmic diseases, in addition to the most widely used indication for chronic heart failure (CHF) (1). New indications of Lewy-body diseases in neurology field were added in the late 1990s.

Prognostic use of ¹²³I MIBG in heart failure

The primary indication listed in the JCS clinical practice guidelines is assessment of severity of heart failure and prognosis for patients with heart failure (Class I: conditions for which there is evidence or general agreement that a given test is useful and effective). Concerning the utility of prognostic evaluation, the studies have unanimously concluded that low values of the heart-to-mediastinum ratio (HMR), a simple average count ratio of cardiac and mediastinal

doi : 10.17996/ANC.01.01.127

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regions, was related to poor prognosis. Another parameter often used was washout rate or MIBG clearance from the heart. The endpoints included cardiac death including deaths from pump failure, sudden cardiac death and acute myocardial infarction, as well as exacerbation of CHF symptoms (2-5). In addition, a number of multicenter studies and meta-analyses have been performed in Japan, Europe and USA (6-10). These studies have indicated that HMR with ¹²³I MIBG had independent and powerful prognostic value. The most appropriate threshold of HMR for discriminating good and poor prognosis has varied among studies, ranging from 1.2 to 1.8 depending on the included patients' background, disease severity, and outcome endpoints, although simple dichotomization of HMR may not be the best practice (11). While CHF symptoms and left ventricular function, and markers such as b-type natriuretic peptide (BNP) are also important predictors of cardiac events, numerous studies have shown that ¹²³I MIBG imaging provides additional prognostic information. It has been more difficult to establish whether MIBG imaging adds clinical value over conventional diagnostic approaches, in spite of its documented additive value over conventional parameters using multiple statistical methods.

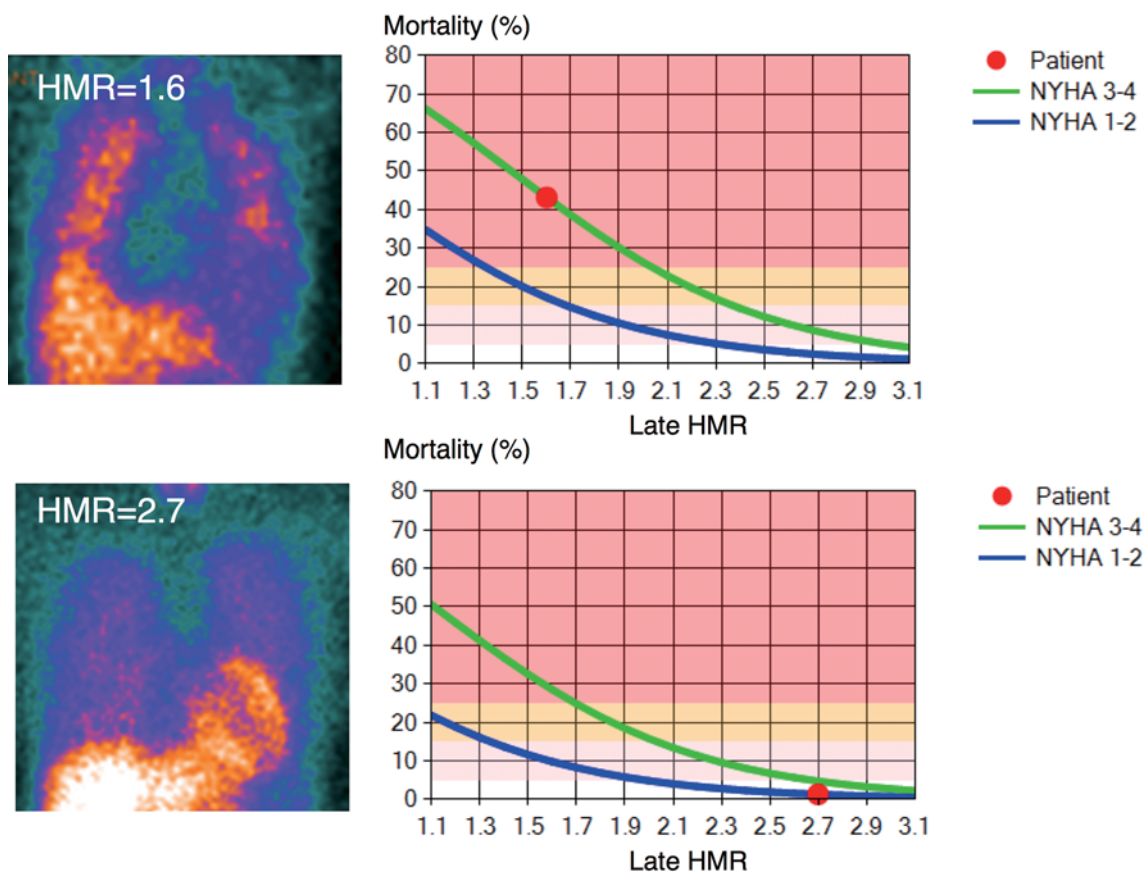
The superiority of the strategy of adding MIBG has been verified using statistical analysis techniques such as multivariate proportional hazards and logistic regression, receiver-operating characteristic curve analysis and net reclassification improvement (NRI) analysis. In the sub-analysis of ADMIRE-HF study, additive value of MIBG was mainly to reclassify patients into severer CHF groups (12). The NRI was 22.7% with 14.9% of subjects who died reclassified into a higher risk category than suggested by Seattle Heart Failure Model score alone. On the other hand, analyses of the Japanese pooled database based on six prospective cohort studies have shown that the model incorporating ¹²³I MIBG could reclassify patients better into the less severe CHF groups compared with the model without MIBG (7). The NRI using the model with ¹²³I MIBG was 17.5% with 10.2% reclassified into lower risks for surviving patients. Although the NRI results from these 2 different patient groups initially appear contradictory, they in fact suggest that the benefits of MIBG imaging may depend on the study population; the potential effective utility of ¹²³I MIBG is in characterizing the dominant component of the CHF population, whether the pretest likelihood of an event in that group is low or high.

Based upon the Japanese meta analysis population, the most potent combination of predictors was New

York Heart Association (NYHA) functional class, age, sex, left ventricular ejection fraction (LVEF), and ¹²³I MIBG HMR (6-8,13) (Fig. 1). Although BNP was also included as a good predictor of cardiac events in these studies, BNP level is known to respond to short-term functional changes, while MIBG is typically relatively stable during hospital course.

¹²³I MIBG for the assessment of medical treatment

The second indication listed in the JCS guidelines is assessment of effect of heart failure treatment (Class IIa: conditions for which there is conflicting evidence or a divergence of opinion about the usefulness of a test, but weight of evidence/opinion is in favor of usefulness). In clinical practice, improvement in symptoms and cardiac function is a salient marker to evaluate therapeutic effects. However, ¹²³I MIBG imaging provides a means to document one of the physiological mechanisms for clinical improvement in CHF patients, recovery of sympathetic neuronal function in response to moderation of sympathetic and renin-angiotensin-aldosterone system overactivity. The research question has been whether improvement of sympathetic function after medications was associated with better clinical course of CHF and eventually related to favorable outcomes. Kasama's review article in this issue of journal, *Annals of Nuclear Cardiology*, summarized the use of ¹²³I MIBG regarding assessment of medical treatments (14). He has extensively investigated the utility of ¹²³I MIBG associated with interventions with medications, including beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone blockers, diuretics, and others. These results indicated that therapeutic interventions affect sympathetic innervation in a variety of ways in addition to the improvement of left ventricular function. As most modern CHF therapeutics act directly or indirectly on the autonomic nervous system and the renin-angiotensin-aldosterone system, the consistent finding of improvement of MIBG cardiac uptake with use of almost all these medications is important validation of their therapeutic effectiveness. However, heart failure treatment guidelines based upon randomized clinical trials do not include MIBG imaging as an adjunct to assist in decision-making. As such, further studies are needed to explore how MIBG could be used to improve decision-making for optimal medical therapy. For example, in almost every clinical trial there is a subset of patients who do not benefit from the therapy under study. Perhaps MIBG imaging would be able to identify such non-responders in clinical practice, thus

**Fig. 1**

^{123}I MIBG studies in two patients with dilated cardiomyopathy (DCM). Upper panel: a 54-year old man with DCM in NYHA class III. ^{123}I MIBG late HMR was 1.6, and LVEF was 19%. The estimated event risk was high: 44% for 5 years (13). In this patient, CRT-D device was implanted and experienced an episode of ventricular tachycardia after MIBG study. Lower panel: a 33-year old woman with DCM in NYHA class II. Her LVEF was 23%, and ^{123}I MIBG late HMR was calculated to be 2.7. The estimated event risk was 1% for 5 years, indicating good prognosis.

avoiding extended courses of ultimately ineffective therapy. At present, cardiologists often think that ^{123}I -MIBG results are interesting but not essential for making treatment decisions. Although ^{123}I MIBG is included in current JCS nuclear cardiology guidelines, ^{123}I MIBG will only be added into cardiology practice guidelines of CHF if further research documents improvement in clinical outcomes among patients who underwent the imaging procedure.

Future directions of ^{123}I MIBG

Standardized methods for data acquisition and processing are required. The method for calculating HMR is simple, but the numerical result is dependent on technical factors that can only be accounted for using cross-calibration techniques to compensate for camera-collimator variations. In Japan, research has been performed on this issue, and more than 100 hospitals are now able to use standardized HMR based on a cross-calibration phantom study (15). Additional studies to

extend the standardization of HMR to cadmium zinc telluride (CZT) cameras, on which conventional anterior planar images cannot be obtained, will also be required.

Despite improvements in therapies over the past several decades, mortality from CHF in Japan, USA and Europe remains high, comparable to that of many types of cancer. Data indicate that the reliability of mortality risk estimation is enhanced using ^{123}I MIBG, allowing more accurate identification of low-risk patients (for example those with HMR >2.0 and annual mortality risk <1%) who are unlikely to benefit from costly cardiac device treatment (Fig. 2). On the other hand, patients who have low HMR and high mortality risk may be more effectively identified for referral for cardiac device therapy such as implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy combined with ICD. In addition, rather than evaluating the effect of medications on individual parameters such as LVEF or MIBG HMR, it might be more appropriate to quantify risk reduction in terms of

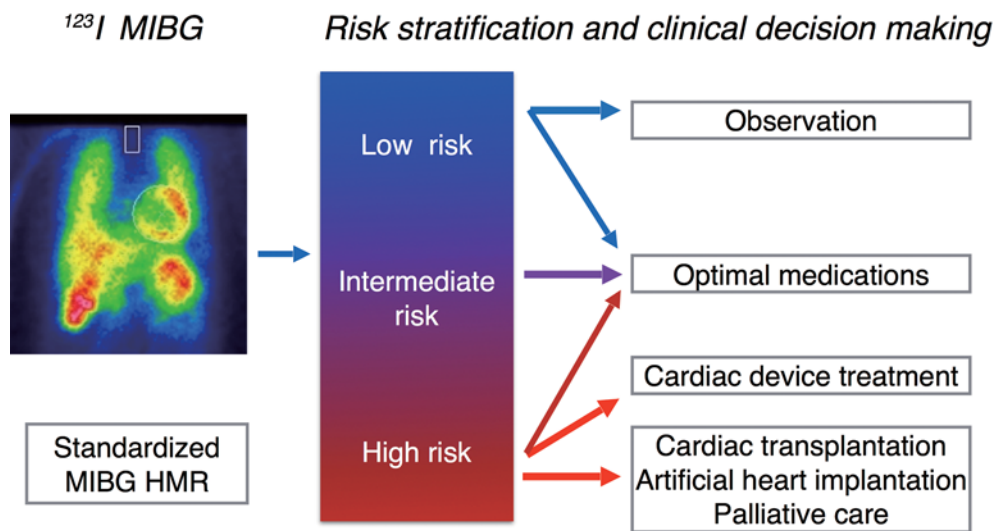


Fig. 2

A possible role of ¹²³I MIBG for clinical decision making. ¹²³I MIBG risk stratification incorporating patient symptoms and parameters; namely, NYHA functional classification, age, sex, LVEF and ¹²³I MIBG HMR, could be used for risk estimation for both low and high-risk patients (13,15).

the estimated mortality rate. Future prospective cohort studies will hopefully confirm the validity of this hypothesis.

In the current era of multimodality imaging, echocardiography, cardiac X-ray computed tomography, and magnetic resonance imaging have specific unique roles to determine etiology and diagnose functional status to aid in the management of CHF. Numerous nuclear cardiology studies, including myocardial perfusion imaging with ECG-gating, fatty acid imaging with ¹²³I beta-methyliodophenyl pentadecanoic acid (BMIPP), ¹⁸F fluorodeoxyglucose (FDG), and ¹²³I MIBG are also available (16). The ongoing challenge for cardiologists and radiologists/nuclear medicine physicians is to select the most appropriate procedures that will yield the necessary clinical information in a cost-effective and patient-centric manner.

Conclusion

¹²³I MIBG imaging is a readily available and powerful tool to predict prognosis in CHF. The next step will be to improve the integration of MIBG imaging into clinical practice in order to enhance effective risk stratification and achieve more cost-effective therapeutic approaches in CHF.

Conflicts of Interest

KN has a collaborative research work for development of the software with FUJIFILM RI Pharma, Co. Ltd, supplier of MyoMIBG in Japan. AJ was formerly employed by GE Healthcare, a manufacturer of MIBG in

Europe and the US.

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