

## ASNC/JSNC JOINT SYMPOSIUM—REVIEW ARTICLE

## Recent Developments and Future Directions of Sympathetic Nervous Function Imaging: MIBG Clinical Aspects in Heart Failure Treatment

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## Abstract

An excess, long-lasting increase in systemic autonomic function facilitates myocardial injury and heart failure (HF), leading to lethal cardiac outcomes. Cardiac <sup>123</sup>I-labeled metaiodobenzylguanidine (MIBG) imaging enables non-invasive and quantitative evaluation of cardiac sympathetic innervation in human hearts. The independent and incremental prognostic values of this imaging technique in combination with clinical information in chronic HF patients have been shown. Results of recent multicenter MIBG studies performed in North-America, Europe and Japan have further strengthened the prognostic values, facilitating the clinical use of cardiac MIBG imaging in long-term management of chronic HF patients. Cardiac neuroimaging can contribute not only to the risk-stratification for lethal events but also to appropriate selection of a therapeutic strategy using drug and device therapies, such as implantable cardioverter defibrillator (ICD) implantation and cardiac resynchronization therapy (CRT), in HF patients. Because of the limitations of current indication criteria, however, some patients undergoing ICD implantation and/or CRT receive no potentially beneficial intervention and, in contrast, some other patients have lethal outcomes without the benefits. Because of increases in medical costs due to non-effective or futile device therapy, the non-negligible number of non-responders to device treatment indicates the need for better selection of high-risk patients who can benefit most from device treatment in a cost-effective manner. Quantitative assessment of cardiac MIBG activity and kinetics can improve the identification of potential candidates for ICD/CRT and reduce costs associated with device treatments with a minimal impact on outcomes. A further large-scale investigation is needed to establish the possibility of cardiac MIBG imaging for more precisely selecting patients at increased risk or at low risk for potentially lethal arrhythmias, sudden cardiac death and/or refractory pump failure so as to optimize therapeutic interventions in patients with heart failure.

**Keywords:** Device treatment, Heart failure, Neuroimaging, Prognosis, Sudden death, Sympathetic function  
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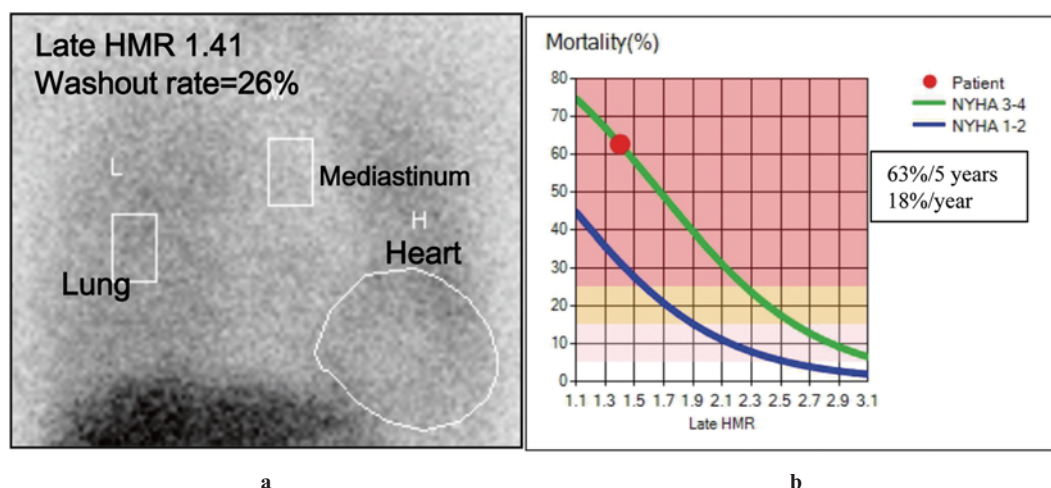
**D**ue to the increasing number of patients with heart failure (HF), advances in HF therapies are needed to establish a more appropriate risk-based therapeutic strategy and cost-effective management for patients with HF. Neuroimaging with <sup>123</sup>I-labeled metaiodobenzylguanidine (MIBG) has been shown to have independent prognostic values that synergistically increase in combination with clinical information such as prior myocardial infarction, New York Heart Association

(NYHA) functional class, left ventricular ejection fraction (LVEF), plasma B-type natriuretic peptide (BNP) and non-cardiac conditions (1-6). Cardiac sympathetic innervation and function can be measured as heart-to-mediastinum ratio (HMR) of cardiac MIBG activity and washout rate of MIBG from the heart, respectively (Fig. 1a). Recent multicenter investigations performed in North-America, Japan and Europe (1-3) have clarified the prognostic values of HMR, possibly

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**Fig. 1** Cardiac neuroimaging with  $^{123}\text{I}$ -labeled metaiodobenzylguanidine in a 73-year-old male with chronic heart failure and NYHA functional class 3 who was admitted due to progression of dyspnea. The patient had a markedly reduced late heart-to-mediastinum ratio (HMR) of MIBG activity but no accelerated washout kinetics (a). He was predicted to have an increased 5-year-mortality rate of 63% (b) and suddenly died 7.5 months later.

facilitating the spread of this imaging technique for long-term HF management in cardiology practice. Thus, cardiac sympathetic innervation assessed by cardiac MIBG imaging is likely to help not only predict the probability of cardiac survival and lethal cardiac events but also select an appropriate therapeutic strategy in patients at greater risk for lethal outcomes due to pump failure or sudden arrhythmic death. This review focuses on clinical implications of cardiac MIBG imaging in pharmacological and non-pharmacological therapeutic interventions in chronic HF patients.

#### Pharmacological treatment and cardiac MIBG imaging

Despite the recent development of evidence-based drug treatment in HF patients with reduced LVEF (HFrEF), therapeutic effects of adrenoceptor blocking agents, renin-angiotensin-aldosterone (RAA) system inhibitors or their combinations on cardiac survival are still limited with a risk reduction rate of only about 20 to 30%. Probable reasons are drug intolerance or adverse effects, progression of myocardial injury due to underlying cardiac diseases and confounding non-cardiac conditions. Many studies (Table 1) have shown that cardiac MIBG activity increases in response to drug treatment using neurohormonal inhibitors in relation to improvement in NYHA class and LVEF during a period of several months but does not increase in non-responders to the treatments (7-18). Cardiac neuroimaging using MIBG can successfully trace alterations of cardiac sympathetic nerve function caused by drug interventions using neurohormonal inhibitors that can exert favorable effects on the cardiac sympathetic system and cardiovascular outcomes in some selected HF patients. It has, therefore, become important clinically to clarify whether the neuroimaging can be useful for selecting an appropriate drug regimen for each HF patient, for predicting therapeutic effects

on clinical outcomes before the start of drug intervention and for predicting survival rate under the condition of drug treatment during long-term management. Our previous study in which 166 HFrEF patients were treated for 43 months (9) showed that treatment with neurohormonal inhibitors significantly reduced the 5-year cardiac mortality rate from 36% to 12% in HFrEF patients in whom HMR was 1.53 or more and from 53% to 37% in HFrEF patients in whom HMR was less than 1.53. The risk reduction rate for cardiac mortality over 5 years in patients with more preserved MIBG activity, therefore, was calculated to be two-times greater than that in those with less MIBG activity: 67% versus 32%,  $p < 0.05$ . Thus, effects of contemporary drug treatment on cardiac mortality depend on cardiac MIBG activity, and improvement in survival rate by drug intervention may be predictable by this method.

#### Implantable cardioverter defibrillator and cardiac MIBG imaging

Sudden cardiac death probably due to lethal ventricular tachyarrhythmias still accounts for a large proportion of deaths in HF patients. Because of the limitations of contemporary drug treatment including amiodarone, implantable cardioverter defibrillator (ICD) is a mainstay for the prevention of sudden cardiac death and has been widely utilized in patients at increased risk for sudden arrhythmic death. Despite the ICD indication based on current guidelines (19), however, some patients die suddenly without any beneficial effect of the ICD. Although multiple factors are involved in the development of refractory lethal arrhythmic events, there is no available biomarker for predicting therapeutic effects by differentiating responders and non-responders to ICD treatment. Alterations of cardiac sympathetic innervation assessed by cardiac

**Table 1** Effects of oral drug interventions on outcomes, cardiac function and/or cardiac MIBG parameters in 12 literatures using 50 or more patients with heart failure

Author, year (Ref. No.)	Patient number	Drugs	Follow-up (months)	Primary End-point		MIBG		Findings	
						Late HMR	WR (%)		
de Millano PA, 2002 (7)	59	Metoprolol	6	Cardiac Function	Placebo Metoprolol			EF:24.8⇒28.1 EF:25.3⇒32.6	
Fujimoto S, 2004 (8)	53	Carvedilol	6-12	Cardiac Function	Carvedilol Metoprolol		48⇒45.6 48⇒52.2	EF:34⇒36 EF:34⇒30	
Nakata T, 2004 (9)	167	ACEI/BB/Both vs Control	43 45	5-year cardiac mortality	ACEI/BB/Both Control	1.68 1.76	38 36	HMR≥1.53 12% vs 36% HMR<1.53 37% vs 53%	
Kasama S, 2005 (10)	50	Candesartan	6	Cardiac Function	Candesartan Placebo	1.87⇒2.00 1.84⇒1.86	37⇒32 38⇒37	EF:54⇒58, BNP:202⇒134 EF:55⇒56, BNP:204⇒193	
Cohen-Solal A, 2005 (11)	64	Carvedilol	6	Cardiac Function	Carvedilol Placebo	1.42⇒1.49 1.46⇒1.43		EF:25⇒31 EF:27⇒28	
Kasama S, 2006 (12)	50	Valsartan Enalapril	6	Cardiac Function	Valsartan Enalapril	1.70⇒1.78 1.68⇒1.67	46⇒41 47⇒46	EF:31⇒39, BNP:237⇒143 EF:32⇒35, BNP:235⇒200	
Kasama S, 2007 (13)	50	Candesartan	6	Cardiac Function	Candesartan +spironolactone Candesartan	1.63⇒1.84 1.68⇒1.76	47⇒46 46⇒41	EF:32⇒43, BNP:249⇒149 EF:31⇒37, BNP:243⇒199	
Tsutamoto T, 2011 (14)	63	Atorvastatin Rosuvastatin	6	Cardiac Function	Atorvastatin Rosuvastatin	2.18⇒2.36 2.26⇒2.25	34.8⇒32.6 31.3⇒31.1	EF:42.8⇒44.3, NT-proBNP:401⇒314 EF:44.2⇒45.1, NT-proBNP:575⇒386	
Kasama S, 2013 (15)	208	Spironolactone	6	Cardiac Function	Spironolactone Control	1.64⇒1.79 1.67⇒1.74	50.5⇒42.4 47.1⇒46.7	EF:33⇒40 EF:32⇒36	
Sano H, 2014 (16)	164	Statin	6	Cardiac Function	Statin Control	1.64⇒1.81 1.66⇒1.74	49.4⇒40.0 47.9⇒45.7	EF:33⇒40 EF:33⇒38	
Kasama S, 2014 (17)	170	Nicorandil	6	Cardiac Function	Nicorandil Control	1.65⇒1.81 1.65⇒1.75	48.7⇒41.5 48.9⇒45.9	EF:33⇒42 EF:33⇒39	
Matsuo Y, 2016 (18)	108	Azosemide Furosemide	6	Cardiac Function	Azosemide Furosemide	1.64⇒1.84 1.63⇒1.70	48.9⇒37.6 49.1⇒47.1	%denervation:58.1⇒44.3 %denervation:60.8⇒55.1	

BB: beta-blockers; EF: ejection fraction; ns: no significant change; NYHA: New York Heart Association; RRR: mortality risk reduction rate.

neuroimaging with MIBG have been shown to be related to lethal ventricular arrhythmias and sudden cardiac death (20-27). Assessment by cardiac MIBG imaging is likely to improve the selection of ICD candidates who can survive by appropriate ICD shock. Reduced cardiac MIBG activity or a larger MIBG defect is an independent predictor of ICD shocks and sudden arrhythmic death. The predictive values increase incrementally with elevated BNP level, reduced LVEF or a large myocardial perfusion defect (25-27) as well as electrophysiological indices (20, 24). In combination with multivariable risk scores of the Seattle Heart Failure Model, cardiac MIBG imaging has additive utility for identifying appropriate candidates for ICD treatment in HF patients (28, 29). Using additional follow-up data from the ADMIRE-HF study, Hachamovitch et al. (30) recently showed that cardiac MIBG imaging can not only improve risk stratification of ICD candidates with HFrEF but also identify actual benefits obtained by successful ablation of lethal arrhythmias with ICD shocks, although HMR data, LVEF or BNP level did not identify patients with improved survival with ICD use. Kawai et al. (31) demonstrated that preserved HMR and low MIBG

washout rate can identify HFrEF patients at a low risk for sudden cardiac death with a positive predictive value of 100%. Thus, assessment of cardiac sympathetic innervation by cardiac neuroimaging in combination with conventional clinical information possibly improves the identification of HFrEF patients at high risk for arrhythmic death for whom an ICD can have beneficial effects on survival.

### Cardiac resynchronization therapy and cardiac MIBG imaging

Cardiac resynchronization therapy (CRT) can improve symptoms and quality of life and reduce recurrent hospitalization in appropriately selected patients with HFrEF who are refractory to contemporary drug treatment, consequently translating to significant reduction in mortality. The current indication for the device treatment depends largely on subjective symptoms (NYHA class), systolic function (LVEF) and QRS duration (32). The limitations of the currently available CRT criteria may be responsible not only for unnecessary use of CRT in non-responders, roughly estimated to be one-third of CRT candidates, but also for underuse of

this device in some patients at high risk for lethal outcomes who can be effectively treated with this device. Among biomarkers proposed, mechanical dyssynchrony and impairment of cardiac sympathetic innervation are noted to be promising for better identification of patients who are most eligible for CRT. Several small studies (33-36) showed that baseline cardiac MIBG activity before introduction of CRT is positively related to an increase in LVEF and a decrease in left ventricular size and that cardiac MIBG activity increases in association with improvement in symptoms, NYHA class and systemic inflammation, indicating that the lower cardiac MIBG activity is or the greater cardiac MIBG washout rate is, the less effective CRT is and the greater the number of non-CRT responders is. Tanaka et al. (37) showed that preserved HMR and mechanical dyssynchrony index can be indicators for the prediction of CRT effects on long-term outcomes. Curcio et al. (38) recently showed that HMR was an independent predictor of response to CRT and predicted new onset HF and re-hospitalization for HF but that echocardiographic LVEF, humoral biomarkers or QRS width did not. Thus, cardiac neuroimaging with MIBG possibly predicts clinical response to CRT, contributing to more appropriate selection of HF patients who can benefit from CRT.

#### Future directions of cardiac neuroimaging with MIBG

Cardiac MIBG imaging is promising not only for predicting response to optimal drug treatment and device treatment but also for better selection of patients who can receive potentially beneficial interventions. It, however, is highly desirable to design a large-scale, multicenter, interventional study. Pre-interventional prediction of therapeutic effects on survival by using cardiac neuroimaging will contribute to the establishment of an appropriate long-term management strategy and also to obviating futile treatment and reducing medical costs on an individual basis together with conventional biomarkers without an unfavorable impact on outcomes. More specifically, there are no clinical data using cardiac MIBG imaging for drug intervention in HF patients with preserved LVEF or for recent novel agents such as dual-acting neurohormonal modulators, vasoactive and anti-inflammatory peptides and myocardial protectants. Using a multiple-cohort database (2), 2-year and 5-year cardiac mortality rates could be predicted using a numerical HMR value in combination with clinical information on an individual basis (Fig. 1b) (39). A future prospective study is needed to determine how cardiac MIBG measurement can be used in clinical practice: for example, for determination of optimal cutoff values of HMR for differentiation of low-risk versus high-risk patients and therapeutic responders versus non-responders to specific treatment and for calculations of prognostic risk score and annual probability of lethal cardiac events with continuous MIBG variables in

cooperation with conventional clinical risks.

#### Conclusions

Impairment of cardiac sympathetic innervation and function estimated by neuroimaging with MIBG can be a powerful prognostic biomarker for selecting heart failure patients at increased risk for lethal arrhythmias, sudden cardiac death and/or refractory pump failure and for predicting prognostic benefits of risk-based drug treatment, ICD and/or CRT, contributing to the optimization of a therapeutic strategy in a more cost-effective manner.

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#### Conflicts of interest

None

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