European Review for Medical and Pharmacological Sciences 2013; 17: 56-68

Clinical usefulness of myocardial innervation imaging using Iodine-123-meta-iodobenzylguanidine scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with heart failure: an overview

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Abstract. – AIM: This study was designed to review published data regarding the clinical usefulness of iodine-123-meta-iodobenzyl-guanidine (MIBG) scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with heart failure (HF).

METHODS: A comprehensive computer literature search of the PubMed/MEDLINE and Embase databases was conducted to find relevant published articles about the clinical usefulness of MIBG scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with HF.

RESULTS: Thirty-three studies, comprising a total sample size of 1124 patients with HF, were included in this review. Main findings of the included studies are presented.

CONCLUSIONS: Myocardial innervation imaging using MIBG scintigraphy can be successfully used to assess changes in cardiac sympathetic neuronal function caused by several pharmacological interventions in patients with HF.

Key Words:
MIBG, Heart failure, Innervation imaging, Pharmacological treatment.

Introduction

Heart failure (HF) is characterized by alterations in myocardial sympathetic nerve activity: an increased sympathetic response is initially favorable by serving as compensation for decreased cardiac output, but as HF progresses this response leads to deleterious neurohormonal and myocardial structural changes that worsen the condition and increase the likelihood of arrhythmias and cardiac death[1].

The pharmacological treatment of HF involves the antagonism of neurohormones that are increased in patients with HF and have harmful effects on the myocardium. Vasodilator treatment and β-adrenergic blockade are the cornerstone of patients with HF.

It has been clearly demonstrated that adrenergic blocking agents, like bisoprolol, metoprolol and carvedilol can improve left ventricular (LV) function and transplant-free survival in patients with HF[2-5].

Among vasodilators, ACE-inhibitors decrease afterload while increasing cardiac output, improve symptoms and survival in patients with LV dysfunction and prevent the development of HF in patients with asymptomatic LV dysfunction and in those at high risk of developing structural heart disease or HF symptoms (coronary artery disease, diabetes mellitus, hypertension)[6-10]. Furthermore, ACE inhibitors are known to increase cardiac β-receptor density and to reduce cardiac sympathetic activity in patients with HF[11].

Although ACE inhibitors decrease the circulating and tissue concentrations of angiotensin II (A-II), the current therapeutic regimens using ACE inhibitors do not adequately suppress A-II production[12]. Several reports have suggested an important role of non-ACE mediated enzymatic pathways in the conversion of angiotensin I to A-II[13,14]. Therefore, the angiotensin receptor blockers (ARBs) appear to be a rational treatment since they reduce mortality and morbidity associated with HF[15].

As aldosterone causes myocardial and vascular fibrosis, direct vascular damage, and baroreceptor dysfunction and prevents myocardial uptake of norepinephrine, aldosterone antagonists have been shown to improve survival and decrease hospitalizations in HF patients[16-20].

Amiodarone has also been reported to improve cardiac performance in patients with HF[21-23] due to

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several effects, including an antifibrillatory effect, the ability to prolong the action potential through alterations in potassium transport, a coronary vasodilatory effect, and a noncompetitive inhibition of α-adrenergic receptors[24,25]. Furthermore, amiodarone can influence thyroid hormone metabolism, which may have cardioprotective effects[26].

Myocardial innervation imaging with iodine-123-meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy provides a noninvasive tool for the investigation of cardiac sympathetic innervation. This technique can also demonstrate drug induced changes in cardiac adrenergic activity[27]. Radiolabeled MIBG is considered an established sympathetic neuron imaging agent useful to study the organs richly innervated by the sympathetic nervous system. MIBG is an analog of guanethidine and is taken up by the postganglionic presynaptic nerve endings of the adrenergic nervous system. After depolarization, MIBG is released into the synaptic cleft like norepinephrine, but is not metabolized. Labeling MIBG with iodine-123 (^{123}I) permits the visualization of adrenergic innervation *in vivo*; MIBG scintigraphy not only displays the presence of noradrenergic innervation but also its functional capability[28,29].

About the scintigraphic method of myocardial innervation imaging, ^{123}I-MIBG is intravenously administered at rest and early (from 10 to 30 minutes after injection) and delayed (from 3 to 4 hours after injection) images are obtained. Planar images with anterior view are adequate for the evaluation of cardiac sympathetic function. Tomographic images (SPECT) are often acquired to evaluate the regional myocardial uptake pattern[28,29].

The most common semi-quantitative indices used for interpretation of myocardial innervation images are the heart to mediastinum ratio (H/M) and the washout rate (WR) obtained from the anterior planar images. Regions of interest (ROIs) are set in the heart (H: target region) and the mediastinum (M: background region) in early and delayed images to obtain the mean count in each ROI, after which the H/M ratio is calculated. Based on the resulting ratio, the degree of accumulation in the heart is evaluated. The WR is an index that indicates the rate at which MIBG is washed out between the early image and the delayed image, via comparison with the cardiac count in the early image. MIBG WR may reflect turnover of catecholamines attributable to the sympathetic drive and measures the ability of myocardium to retain MIBG. Normal values of these indices have been calculated performing MIBG scintigraphy in control patients and are different between various institutions depending on acquisition conditions[28,29]. A recently reported normal value for H/M ratio is 2.2 ± 0.3, with a ratio of 1.6 (2 standard deviations below the mean) considered to be abnormal [1]. MIBG WR may reflect turnover of catecholamines attributable to the sympathetic drive, and measures the ability of myocardium to retain MIBG. A normal value has been reported to be 10% ± 9%, with sicker patients having higher values[1].

Increased sympathetic activity in HF is associated with high myocardial MIBG WR and low myocardial MIBG early and delayed H/M[1,27,29].

Since semiquantitative analysis of cardiac MIBG uptake is characterized by a low interindividual and a within-subject variability[30], semiquantitative indices of MIBG scintigraphy have become valuable tools to provide information regarding the potential and actual benefit of therapeutic interventions in patients with HF[31].

Several studies have shown that assessment of the cardiac autonomic state with ^{123}I-MIBG scintigraphy can help to assess the prognosis and to monitor the effects of therapeutic interventions in HF patients[27]. However, an overview of published data regarding the clinical usefulness of MIBG scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with HF is lacking.

Methods

Search Strategy

A comprehensive computer literature search of the PubMed/MEDLINE and Embase databases was conducted to find relevant published articles on the clinical usefulness of MIBG scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with HF. We used a search algorithm that was based on a combination of the terms: (1) "MIBG" or "metaiodobenzylguanidine" and (2) "heart failure". No beginning date limit was used; the search was updated until 31 December 2010. No language restriction was used. To expand our search, references of the retrieved articles were also screened for additional studies.

Study Selection

Studies or subsets in studies investigating the clinical usefulness of MIBG scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with HF were eligible for inclu-

sion. Review articles, editorials or letters, comments, conference proceedings and case reports were excluded from this review.

Only those studies or subsets in studies that satisfied all of the following criteria were included: (1) MIBG scintigraphy performed in patients with HF; (2) MIBG scintigraphy performed before and after pharmacological treatment to evaluate its effectiveness.

The exclusion criteria were: (1) overlap in the patient data (duplicate publication); in such cases, the most complete article was included; (2) MIBG scintigraphy not performed before and after pharmacological treatment.

Two researchers (GT and AS) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data Abstraction

For each included study, informations were collected concerning basic study (author names, journal, year of publication, country of origin), patient characteristics (mean age, sex, number of patients which performed MIBG scintigraphy), pharmacological treatment assessed, semiquantitative MIBG parameters evaluated (as early H/M, delayed H/M, WR or regional myocardial uptake) and timing of MIBG scintigraphy (before and after treatment). Main findings of each study included in this review are summarized in the text.

Results

Literature Search

The comprehensive computer literature search from the PubMed/MEDLINE and Embase databases revealed 304 articles (Figure 1). Reviewing titles and abstracts, 265 articles were excluded because data were not within the field of interest of this review; 39 articles were selected. These studies were retrieved in full text version; no additional study was found screening the references of these articles. From these 39 articles potentially eligible for inclusion, after reviewing the full text article, one study was excluded because there was an overlap of patient data in another study and the most complete article was included[32,33]; five articles were excluded because MIBG scintigraphy was not performed before and after pharmacological treatment in patients with HF[34-38].

Finally, 33 studies, comprising a total sample size of 1108 patients with HF, met all inclusion and exclusion criteria, and they were included in this review[32,39-70]. The characteristics of the included studies are presented in Tables I and II.

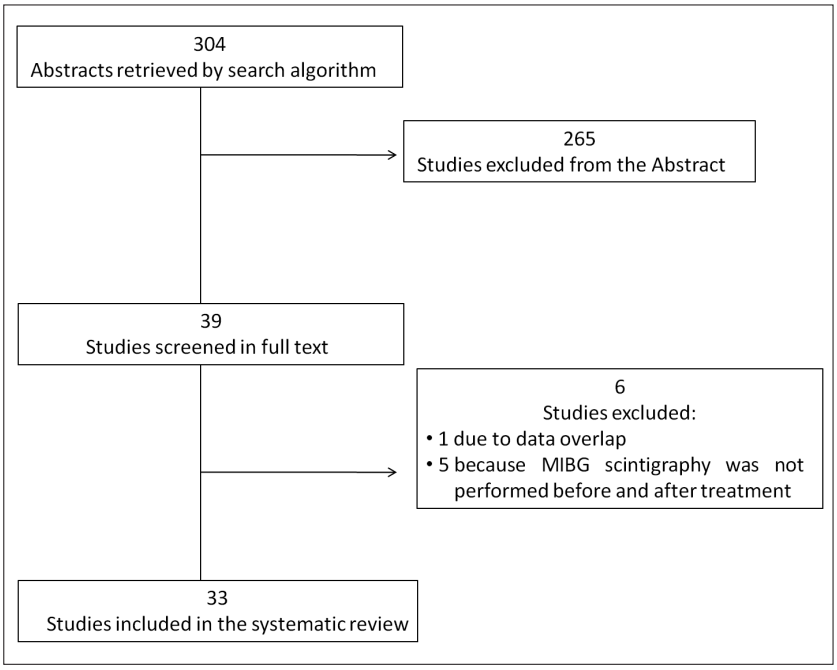

Figure 1. Flow chart of the search for eligible studies on the usefulness of MIBG scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with heart failure.

Table I. General characteristics of patients in the included studies.

Authors	Year	Journal	Country	N. of patients	Mean age (years)	% male
Eichhorn EJ et al[53]	1991	Am J Cardiol	USA	15	50 ± 11	100%
Barr CS et al[64]	1995	Am J Cardiol	United Kingdom	28 + 14C	68 ± 3	79%
Somsen GA et al[55]	1996	Heart	The Netherlands	23	60 ± 10	70%
Fukuoka S et al[39]	1997	Eur J Nucl Med	Japan	13 + 7C	43 ± 13	85%
Takeishi Y et al[56]	1997	J Nucl Med	Japan	29	59	79%
Kakuchi H et al[40]	1999	Heart	Japan	27	52.2	78%
Soeki T et al[57]	1998	Jpn Heart J	Japan	10	62 ± 11	70%
Toyama T et al[52]	1999	J Nucl Med	Japan	24	58 ± 12	58%
Fujimura M et al[42]	2000	J Card Fail	Japan	42	50 ± 12	81%
Agostini D et al[43]	2000	J Nucl Med	France	22 + 10C	54	86%
Lotze U et al[48]	2001	J Nucl Med	Germany	10	51 ± 8	90%
Yamazaki J et al[44]	2001	Am Heart J	Japan	58 + 17C	54 ± 11	88%
Hirooka K et al[45]	2001	Jpn Circ J	Japan	91	49	81%
Takeda N et al[70]	2001	Exp Clin Cardiol	Japan	34	58	65%
Shinohara H et al[60]	2002	Heart Vessels	Japan	34	70 ± 10	82%
de Milliano PA et al[41]	2002	Am Heart J	The Netherlands	54	65	67%
Kasama S et al[65]	2002	J Nucl Med	Japan	30	69 ± 13	57%
Gerson MC et al[47]	2002	J Nucl Cardiol	USA	22	48.4 ± 8.5	68%
Kasama S et al[66]	2003	J Am Coll Cardiol	Japan	30	65 ± 15	57%
Kasama S et al[61]	2003	J Nucl Med	Japan	32	68 ± 12	59%
Toyama T et al[46]	2003	J Nucl Med	Japan	30	59 ± 12	77%
Fujimoto S et al[32]	2004	Eur J Nucl Med Mol Imaging	Japan	53	56.5 ± 10.9	81%
Toyama T et al[68]	2004	J Nucl Cardiol	Japan	30	57 ± 13	77%
Kasama S et al[62]	2005	J Am Coll Cardiol	Japan	50	66.3	66%
Kasama S et al[58]	2005	Eur J Nucl Imaging Med Mol	Japan	40	69.5	72%
Cohen-Solal et al[49]	2005	J Nucl Med	France	50	59 ± 10	84%
Kasama S et al[63]	2006	Heart	Japan	50	68 ± 9	62%
Chizzola PR et al[50]	2006	Int J Cardiol	Brazil	22	44.5	68%
Kasama S et al[51]	2007	Eur Heart J	Japan	30 +10C	55 ± 11	67%
Kasama S et al[67]	2007	J Nucl Med	Japan	50	68	66%
Toyama T et al[69]	2008	J Nucl Cardiol	Japan	30	59 ± 9	80%
Tsutamoto T et al[59]	2008	Circ J	Japan	45	57.3	87%
de Miranda SM et al[54]	2010	Arq Bras Cardiol	Brasil	16	56.3 ± 12.6	69%

Legend: C = normal controls

Report of Literature Data

In the last years several clinical trials, using MIBG scintigraphy, have reported a beneficial effect of beta-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists and other drugs on cardiac sympathetic activity in HF setting.

Beta-Blockers

Several trials have demonstrated an improvement of cardiac sympathetic function assessed by MIBG scintigraphy in patients with HF treated with β-blockers.

The first trials conducted to detect any change in myocardial adrenergic nervous system after introduction of β-blocker treatment, have used metoprolol. As the functional improvement provided by β-blocker treatment takes more than 2 months, Fukuoka et al[39] investigated whether MIBG scintigraphy could be used to predict drug effectiveness. Thirteen patients with dilated cardiomyopathy (DCM) were studied and classified into those showing a ≥ 5% increase in LV ejection fraction (LVEF) at 3 months compared with LVEF values before the treatment with metoprolol (group I, n=7) and those showing a < 5% increase in LVEF (group II, n=6). This study

Table II. General characteristics of methods in the included studies.

Authors	Year	Pharmacological treatment assessed	MIBG parameters evaluated	Timing of MIBG scintigraphy
Eichhorn EJ et al[53]	1991	Bucindolol 12.5 up to 100 mg/day	Regional MIBG uptake	Before and 3 months after treatment
Barr CS et al[64]	1995	Spironolactone 50 up to 100 mg/day vs placebo	H/M[d]	Before and 8 weeks after treatment
Somsen GA et al[55]	1996	Enalapril 2.5 up to 10 mg/day	Myocardial MIBG uptake	Before and 6 weeks after treatment
Fukuoka S et al[39]	1997	Metoprolol 5 up to 40 mg/day	Global WR, regional WR, H/M[d]	Before, 1 month and 3 months after treatment
Takeishi Y et al[56]	1997	Enalapril 5 up to 10 mg/day vs conventional treatment	H/M[e], H/M[d], WR	Before and 9.1 ± 3 months after treatment
Kakuchi H et al[40]	1999	Metoprolol 5 up to 40 mg/day	H/M[e], H/M[d], WR	Before, 1 month and 3 months after treatment
Soeki T et al[57]	1998	Enalapril 2.5-5 mg/day	H/M[e], H/M[d], WR	Before and 3 to 15 months after treatment
Toyama T et al[52]	1999	Metoprolol 2.5-5 up to 30-60 mg/day vs enalapril 5-10 mg/day	H/M[d], WR, regional uptake score	Before, 5 months and 1 year after treatment
Fujimura M et al[42]	2000	Carvedilol 2.5 up to 20 mg/day	H/M[e], H/M[d], WR	Before and 3 to 5 months after treatment
Agostini D et al[43]	2000	Carvedilol 12.5 up to 50 mg/day	H/M[d] ratio	Before and 6 months after treatment
Lotze U et al[48]	2001	Carvedilol 3-50 mg/day, metoprolol 5-150 mg/day or bisoprolol 1.25-10 mg/day	Myocardial to ventricular c avity ratio	Before and 1 year after treatment
Yamazaki J et al[44]	2001	Nipradilol 1.5-9 mg/day, metoprolol 2.5-120 mg/day or carvedilol 2.5-20 mg/day	WR, regional uptake scores	Before and 6 months after treatment
Hirooka K et al[45]	2001	Metoprolol 5 up to 40 mg/day vs carvedilol 2.5 up to 20 mg/day	H/M[e], H/M[d], WR	Before and 3 months after treatment
Takeda N et al[70]	2001	Pimobendan 2.5 mg/day	H/M[d], WR	Before and 12 months after treatment
Shinohara H et al[60]	2002	Losartan up to 25-50 mg/day or candesartan up to 4-8 mg/day	H/M[e], H/M[d], WR	Before and 6 months after treatment
de Milliano PA et al[41]	2002	Metoprolol 25 up to 150 mg/day vs placebo	Myocardial MIBG uptake	Before and 6 months after treatment
Kasama S et al[65]	2002	Spironolactone 12.5-50 mg/day vs conventional treatment	H/M[d], WR, regional uptake score	Before and 6 months after treatment
Gerson MC et al[47]	2002	Carvedilol 6.25 up to 50-100 mg/day	H/M[e], H/M[d], WR	Before and 7.2 ± 2.7 months after treatment
Kasama S et al[66]	2003	Spironolactone 25 mg/day vs conventional treatment	H/M[d], WR, regional uptake score	Before and 6 months after treatment
Kasama S et al[61]	2003	Valsartan 40-80 mg/day vs conventional treatment	H/M[d], WR, regional uptake score	Before and 6 months after treatment
Toyama T et al[46]	2003	Carvedilol 1.25-2.5 up to 10-20 mg/day vs metoprolol 2.5-5 up to 30-60 mg/day	H/M[d], WR, regional uptake score	Before and 1 year after treatment
Fujimoto S et al[32]	2004	Nipradilol, metoprolol or carvedilol	WR, extent score, severity score	Before and within 1 year after treatment
Toyama T et al[68]	2004	Metoprolol 2.5-5 up to 30-60 mg/day vs amiodarone 100 mg/day	H/M[d], WR, regional uptake score	Before and 1 year after treatment
Kasama S et al[62]	2005	Candesartan 2-4 up to 8-12 mg/day vs placebo	H/M[d], WR, regional uptake score	Before and 6 months after treatment
Kasama S et al[58]	2005	Perindopril 2 mg/day vs enalapril 5 mg/day	H/M[d], WR, regional uptake score	Before and 6 months after treatment
Cohen-Solal et al[49]	2005	Carvedilol 6.5 up to 50-100 mg/day vs placebo	H/M[d], WR, regional uptake, extent and severity score	before and 6 months after treatment

Table continued

Table II *(Continued)*. General characteristics of methods in the included studies.

Authors	Year	Pharmacological treatment assessed	MIBG parameters evaluated	Timing of MIBG scintigraphy
Kasama S et al[63]	2006	Valsartan 80 mg/day vs enalapril 5 mg/day	H/M[d], WR, regional uptake score	Before and 6 months after treatment
Chizzola PR et al[50]	2006	Carvedilol 12.5 mg/day up to 75 mg/day vs placebo	H/M[e], H/M[d]	Before, 2 months and 6 months after treatment
Kasama S et al[51]	2007	Carvedilol 1.25-2.5 up to 10-20 mg/day	H/M[d], WR, regional WR, regional uptake and defect score	Before and 12 ± 1 months after treatment
Kasama S et al[67]	2007	Candesartan 2-4 up to 8-12 mg/day plus spironolactone 25 mg/day vs candesartan alone	H/M[d], WR, regional uptake score	Before and 6 months after treatment
Toyama T et al[69]	2008	Carvedilol 1.25-2.5 up to 10 mg/day Plus amiodarone 100 mg/day vs carvedilol alone	H/M[d], WR, regional uptake score	Before and 1 year after treatment
Tsutamoto T et al[59]	2008	Continuous enalapril 10 mg/day vs switching to perindopril 4 mg/day	H/M[d], WR	Before and 6 months after treatment
de Miranda SM et al[54]	2010	Carvedilol 30 mg/day	H/M[e], H/M[d], WR	Before and 6 months after treatment

Legend: e H/M: early heart to mediastinum ratio; d H/M: delayed heart to mediastinum ratio; WR: washout rate.

demonstrated that during β-blocker treatment in patients with DCM in all segments, except the inferior segment, regional MIBG washout improved earlier than either the global indices or LV function, and that the global MIBG WR improved simultaneously with LV function. These results suggest that regional assessment with myocardial MIBG scintigraphy provides early prediction of functional improvement due to β-blocker treatment in patients with DCM.

Kakuchi et al[40] studied patients affected by DCM, who were classified into 2 groups, based on whether they reached a daily dose of > 20 mg of metoprolol without deterioration of HF at three months (group A) or not (group B). At baseline MIBG myocardial uptake was higher, and the MIBG WR lower, in group A than in group B although no significant differences in the echocardiographic indices or neurohormonal activity between the two groups were found. After one month, though there were no significant changes in echocardiographic and neurohormonal variables, the MIBG H/M ratio on the delayed image was increased in group A but not in group B. In group A, the degree of increase of delayed H/M ratio one month after treatment was also correlated with the degree of reduction in plasma concentrations of noradrenaline after three months, confirming the benefit of β-blocker treatment on cardiac nervous system.

de Milliano et al[41] studied 59 patients with HF randomized to their maximal tolerable dose of metoprolol or placebo; the Authors found a 21.9% increase in mean myocardial MIBG uptake after 6 months of treatment with metoprolol. In contrast, myocardial MIBG uptake decreased by 7.8% in the placebo group ($p = 0.03$ compared with metoprolol group). LV end-diastolic diameter decreased significantly ($p < 0.05$, within-group comparison) and LVEF increased ($p < 0.05$, within-group comparison) in the metoprolol group. Placebo-treated patients showed no significant changes.

It has been widely demonstrated that carvedilol can induce important clinical and hemodynamic improvements in patients with HF resulting from severe LV dysfunction. First Fujimura et al[42] divided 42 patients with DCM into 2 groups: 27 responders to carvedilol whose LVEF increased by more than 5% and 15 nonresponders to carvedilol whose LVEF increased by 5% or less. Although MIBG image-derived indexes of nonresponders remained unchanged, the delayed H/M (from 1.91 ± 0.34 to 2.24 ± 0.53, *p*

< 0.01) and WR (from 49 ± 11 to 39 ± 9%, $p <$ 0.01) of responders improved after treatment with carvedilol. Thus this trial proved that carvedilol treatment ameliorates LVEF and neurohumoral factors.

Agostini et al[43] also examined the impact of carvedilol on cardiac neuronal function in patients with DCM. Twenty-two patients with HF assessed as New York Hospital Association (NYHA) class II or III and with initial resting radionuclide LVEF < 40% were enrolled in the study. After carvedilol treatment NYHA functional classification for these patients improved from 2.6 ± 0.5 to 2.3 ± 0.5 ($p = 0.04$), LVEF improved from 22% ± 9% to 30% ± 13% ($p = 0.005$), and MIBG delayed H/M ratio improved from 145% ± 23% to 170% ± 25% ($p = 0.0001$). This data confirmed that carvedilol induces improvement of clinical symptoms and cardiac neuronal and systolic functions in patients with DCM and optimal chronic treatment.

Yamazaki et al[44] studied 58 patients with DCM and found a significant correlation between LVEF and MIBG indices (regional uptake scores and WR) obtained before and 6 months after β-blocker treatment (nipradilol, metoprolol or carvedilol). After β-blocker treatment, LVEF and MIBG indices significantly improved in group A, in which LVEF improved by 10% or more within 6 months after treatment. On the other hand, no change occurred in MIBG indices in group B (defined as less than a 10% change in LVEF). Regard to the efficacy of single β-blocker molecules on cardiac nervous system, both metoprolol and carvedilol, when tolerated, improved cardiac function and neurohumoral factors to the same degree.

However, carvedilol is preferable to metoprolol for patients with a low delayed H/M ratio as Hirooka et al[45] showed. These Authors found that drug intolerance occurred in 24% of patients treated with metoprolol (7 of 29) and 19% of patients treated with carvedilol (10 of 62). Moreover, in the drug-tolerant patients the percentage of patients with a delayed H/M ratio below 1.9 in the carvedilol group was significantly higher than that in the metoprolol group. This study confirmed that both metoprolol and carvedilol, when tolerated, improved cardiac function. Nevertheless metoprolol must be administered carefully when the delayed H/M ratio is low, whereas carvedilol can often be given in such circumstances.

A following study by Toyama et al[46] compared 15 patients with DCM who were receiving carvedilol (group A) to 15 patients with DCM who were receiving metoprolol (group B). In both groups, the delayed H/M increased (in group A, from 1.67 ± 0.31 to 2.01 ± 0.36, $p < 0.01$; in group B, from 1.68 ± 0.21 to 1.93 ± 0.32, $p < 0.01$). This study demonstrated that carvedilol treatment improved cardiac function, symptoms, and cardiac sympathetic nerve activity in patients with DCM to a similar extent as metoprolol treatment and the improvement of cardiac function and symptoms was related to the improvement of cardiac sympathetic nerve activity.

Gerson et al[47] confirmed that carvedilol treatment reduces the mortality rate and improves cardiac sympathetic nervous function in patients with HF. In 22 HF patients with idiopathic cardiomyopathy, sympathetic nerve function was assessed before and after 7.2 ± 2.7 months of carvedilol treatment with the use of ^{123}I-MIBG imaging. Patients with relatively advanced impairment of cardiac sympathetic nerve function, as manifested by a baseline MIBG H/M ratio lower than 1.40, had a statistically significant improvement in H/M ratio with carvedilol treatment, from 1.26 ± 0.12 to 1.39 ± 0.20 ($p = 0.004$). These Authors demonstrated that patients with advanced impairment of baseline MIBG uptake were most likely to show evidence of improved cardiac sympathetic nervous system function in response to carvedilol treatment. Furthermore a favorable response of LVEF to carvedilol was apparent in all study patients regardless of the level of impairment of baseline cardiac neuronal function. The findings of this investigation are consistent with those of previous publications, including a study by Lotze et al[48] which showed improvement in the myocardial MIBG uptake after treatment with various β-adrenergic blockers including metoprolol, carvedilol and bisoprolol.

Fujimoto et al[32] investigated the usefulness of cardiac MIBG imaging in predicting cardiac events in 53 patients with DCM. The Authors demonstrated that the degree of improvement in MIBG WR after introduction of β-blockers (including metoprolol, carvedilol or nipradilol) was a significant predictor of cardiac events. DCM patients who would benefit the most from β-blocker treatment were those with high WR before β-blocker introduction regardless of LVEF values.

In the last years several trials have confirmed previous results. Cohen-Solal et al[49] conducted a clinical trial on 64 HF patients who underwent measurements of cardiac sympathetic activity, circulating catecholamine level, and hemodynamic indices before and after 6 months of treat-

ment with either carvedilol or placebo. Beyond the well-known effects on cardiac function of carvedilol, an increase in myocardial MIBG uptake was found by both planar and tomographic imaging ($p < 0.01$). End-diastolic and end-systolic LV diameters decreased (both $p < 0.05$) and LVEF increased ($p < 0.03$) in the carvedilol group, whereas these parameters remained unchanged in the placebo group. The benefits of carvedilol on resting hemodynamics appeared to be associated with a partial recovery of cardiac adrenergic innervation functioning without detectable antioxidant effect in the plasma.

Chizzola et al[50] showed a trend of gradual improvement in cardiac sympathetic function (as indicated by the improved myocardial uptake of MIBG in early and delayed images) when carvedilol was added to standard HF treatment and compared to placebo in patients with DCM.

In 2007 Kasama et al[51] studied the influence of carvedilol on cardiac sympathetic function and LV remodelling in 30 patients with DCM and 10 normal controls. Both MIBG scintigraphic parameters and echocardiographic parameters (as LV end-diastolic volume and LV end-systolic volume) were improved in the DCM patients. There was a significant correlation between the changes of MIBG scintigraphic and echocardiographic findings after treatment.

Some Authors reported that β-blockers are more effective on the cardiac nervous system than other drugs widely used for HF treatment. Toyama et al[52] studied 24 patients with DCM, comparing the effect of metoprolol and ACE-inhibitors on cardiac sympathetic function assessed by MIBG scintigraphy. Although delayed H/M one year after therapies was increased in both groups (in patients treated with metoprolol from 1.87 ± 0.31 to 2.14 ± 0.29; $p < 0.01$; in patients treated with enalapril from 1.82 ± 0.28 to 1.94 ± 0.26; $p < 0.05$), it was more improved by β-blockers than by ACE-inhibitors ($p < 0.05$). However, a possible explanation for the inadequate improvement of the cardiac sympathetic function with ACE inhibitors may lay on the insufficient dosage (5-10 mg/day), which was not stepped up to its maximum.

Lastly, only two trials[53,54], using bucindolol and carvedilol respectively, have not been able to demonstrate a beneficial effect of β-blocker treatment on myocardial sympathetic function assessed by MIBG scintigraphy, probably because the treatment duration was shorter and the beta-blocker dose used was lower than that used in other studies.

ACE-Inhibitors

Some Authors demonstrated an improvement of cardiac sympathetic function assessed by MIBG scintigraphy in patients with HF treated with ACE inhibitors.

Somsen et al[55] studied 23 consecutive patients with chronic, mild to moderate, stable congestive HF and a LVEF less than 40%. MIBG scintigraphy was performed and plasma noradrenaline concentration was measured before and 6 weeks after treatment with enalapril. Myocardial uptake of MIBG increased significantly after enalapril treatment, indicating improved cardiac sympathetic function ($p < 0.02$). However, myocardial MIBG uptake was not related to plasma noradrenaline concentration. This trial showed that enalapril improves cardiac sympathetic neuronal uptake function in a group of patients with predominantly moderate heart failure, behind its effect on blood pressure lowering and on cardiac remodeling. These results agree with the hypothesis that restoration of cardiac neuronal uptake of noradrenaline is one of the beneficial effects of enalapril.

These findings were confirmed by other studies. Takeishi et al[56] investigated 29 patients, NYHA functional class II-III, receiving conventional treatment for HF; 19 patients received additional treatment with enalapril and 10 patients were treated with conventional treatment alone and were defined as a control group. In the enalapril group, the MIBG H/M ratio was increased after treatment (early H/M ratio: from 1.60 ± 0.22 to 1.73 ± 0.28, $p < 0.05$; delayed H/M ratio: from 1.63 ± 0.28 to 1.82 ± 0.33, $p < 0.01$) and MIBG WR was reduced after treatment (from 38% ± 11% to 30% ± 12%, $p < 0.01$). However, in the conventional treatment group, the H/M ratios in the early and delayed images and WR remained unchanged after treatment. In patients of enalapril group with an increased H/M ratio (n = 13), LVEF increased from 48% ± 12% to 55% ± 9% ($p < 0.01$) after treatment.

Soeki et al[57] showed that MIBG H/M ratio increased significantly (early H/M: from 1.99 ± 0.38 to 2.20 ± 0.50; delayed H/M: from 1.86 ± 0.44 to 2.09 ± 0.51) and MIBG WR decreased slightly (from 29.1 ± 9.1% to 25.4 ± 7.0%) when patients with HF were treated with 2.5-5.0 mg of enalapril once a day for 3-15 months.

Among ACE inhibitors, perindopril seems to be more effective in the improvement of cardiac sympathetic function as Kasama et al[58] demonstrated in 40 patients with HF (LVEF < 45%) who were randomly assigned to perindopril (2

mg/day; n=20) or enalapril (5 mg/day; n=20). All patients were also treated with diuretics. Six months after treatment with perindopril, delayed H/M ratios increased from 1.62 ± 0.27 to 1.76 ± 0.29 ($p < 0.01$), WR decreased from 50 ± 14% to 42 ± 14% ($p < 0.05$). In contrast, in patients receiving enalapril, there was no significant difference between the values at baseline and 6 months after treatment.

These data were confirmed by Tsutamoto et al[59] in 2008. Forty-five stable HF patients undergoing conventional treatment including enalapril were randomized in 2 groups [group I (n=24): continuous enalapril treatment; group II (n=21): enalapril switched to perindopril]. Six months after treatment, in group I there were no changes in MIBG parameters, LVEF or plasma level of brain natriuretic peptide. In contrast, in group II the delayed MIBG H/M ratio was significantly increased (from 2.0 ± 0.07 to 2.15 ± 0.07, $p = 0.013$) and the MIBG WR was significantly decreased compared with the baseline value (from 33.0 ± 1.4 to 30.5 ± 1.2, $p = 0.03$). Unlike the previous trial designed by Kasama et al[58], the present study compared the effects of switching from enalapril to perindopril on stable patients with HF who have already received standard treatment including carvedilol and spironolactone. This suggests that perindopril is superior to enalapril and may exert a favorable effect on cardiac sympathetic system as well as on cardiovascular outcomes.

Angiotensin Receptor Blockers (ARBs)

First of all, the trial of Shinohara et al[60] investigated the efficacy of ARBs against cardiac sympathetic overactivity using MIBG scintigraphy in patients with HF. These Authors studied 34 HF patients treated with losartan or candesartan with fractional shortening of the LV diameter ≤ 25% or LVEF ≤ 45%. MIBG scintigraphy performed before and 6 months after ARBs treatment revealed that ARBs did not significantly change the delayed H/M ratio. However, the MIBG WR fell significantly (from 32.6% ± 7.6% to 28.2% ± 7.5%; $p < 0.001$) suggesting the efficacy of these agents in modifying cardiac sympathetic function in patients with HF.

It has been clearly demonstrated that ARBs can improve cardiac sympathetic nerve activity in patients with HF, when these drugs are added to an ACE-inhibitors. Kasama et al[61] studied 32 patients with HF (LVEF < 40%) treated with an ACE inhibitor and a loop diuretic. Sixteen patients (group A) were randomized to additionally receive valsartan (40-80 mg/day), and the remaining 16 patients (group B) continued their current regimen. Patients were studied before and 6 months after treatment. After treatment in group A, delayed H/M ratio increased from 1.66 ± 0.23 to 1.81 ± 0.23 ($p < 0.001$), and WR decreased from 47% ± 9% to 39% ± 10% ($p < 0.01$); in addition, the LV end-diastolic volume decreased and LVEF increased. In group B, these parameters did not change significantly.

Moreover, ARBs seem to be beneficial on cardiac sympathetic nerve activity in patients with HF with a preserved LVEF as Kasama et al found in 2005[62]. They selected 50 patients with non-ischemic HF and LVEF > 40% who were treated with standard treatment. Twenty-five patients were randomized to also receive candesartan, whereas the remaining 25 patients received placebo. In patients receiving candesartan, MIBG scintigraphic and echocardiographic parameters were significantly improved 6 months after treatment. In contrast, there were no significant changes of these parameters in patients receiving placebo. These findings suggest that addition of candesartan to an ACE inhibitor may result in stronger inhibition of renin-angiotensin-aldosterone system, increase of myocardial uptake of norepinephrine and improvement of LV performance in HF patients with preserved LVEF.

The same investigators also showed that ARBs treatment alone improves cardiac nervous system function compared to ACE-inhibitors. Six months after treatment, in patients receiving valsartan MIBG delayed H/M ratio increased from 1.70 ± 0.17 to 1.78 ± 0.22 ($p < 0.05$) and MIBG WR decreased from 46% ± 11 to 41% ± 10 ($p < 0.05$). However, these parameters did not change significantly in patients receiving enalapril[63].

Aldosterone Antagonists

Several trials have been designed to assess cardiac sympathetic system improvement in patients with HF on chronic treatment with aldosterone receptor blockers (like spironolactone).

First of all, Barr et al[64] demonstrated that myocardial MIBG uptake increased in HF patients treated with spironolactone in comparison with patients treated with placebo.

Kasama et al[65] also investigated the effects of spironolactone on MIBG parameters. Thirty patients with HF (LVEF < 40%), treated with an ACE-inhibitor, a loop diuretic, and, in most cases, digoxin were divided into 2 groups: 15 patients (group A) were assigned to additionally re-

ceive spironolactone (12.5-50 mg/day), and the remaining 15 patients (group B) continued their current regimen. Six months after treatment, in group A MIBG delayed H/M ratio increased from 1.62 ± 0.20 to 1.83 ± 0.27 ($p < 0.0001$), and MIBG WR decreased from 51 ± 9 to 40 ± 15 ($p < 0.001$). By contrast, in group B these parameters did not significantly change.

These results were confirmed in a following study from the same investigators[66], conducted in 30 patients with DCM who were randomly assigned to spironolactone or conventional treatment; in the spironolactone group delayed H/M ratio increased from 1.64 ± 0.20 to 1.86 ± 0.27 ($p < 0.0001$), and WR decreased from 55 ± 12% to 41 ± 15% ($p < 0.0005$). Furthermore, in this group echocardiographic parameters (LVEF and LV end-diastolic volume) ameliorate significantly. There were no significant changes in these parameters in the control group.

In 2007 Kasama et al[67] focused their attention on the effects of a combined treatment with spironolactone and candesartan compared to candesartan alone on cardiac nervous system and LV performance. Fifty patients with HF (LVEF < 45%) were randomly assigned to candesartan plus spironolactone (group A; n=25) or to candesartan alone (group B; n=25). All patients were also treated with a loop diuretic. After 6 months, all MIBG scintigraphic and echocardiographic parameters (LVEF, LV end-diastolic volume, LV end-systolic volume) were improved in both groups. However, the degree of change of these parameters after treatment tended to be better in group A than in group B. In this study there were also significant correlations between changes in the LV volume and the MIBG scintigraphic parameters only in group A. However, it is still unclear whether improvement of LV function (due to the antifibrotic effect of spironolactone) increases myocardial uptake of norepinephrine or whether increased myocardial uptake of norepinephrine leads to improvement in LV function.

Other Drugs

Some Authors investigated whether amiodarone may exert some effects on cardiac nervous system in patients with HF using MIBG scintigraphy.

In 2004 Toyama et al[68] compared 15 patients with DCM receiving amiodarone (group A) with 15 patients receiving metoprolol (group B). One year after treatment, in both groups MIBG scintigraphic parameters and echocardiographic LVEF ameliorate, suggesting that amiodarone can improve cardiac sympathetic nerve activity as well as β-blockers do.

Moreover, the same Authors[69] demonstrated that combined treatment with carvedilol plus amiodarone was more effective than carvedilol alone on cardiac sympathetic activity in patients affected by DCM. Combined treatment improved several MIBG scintigraphic and echocardiographic parameters much more than carvedilol alone. Several mechanisms are responsible of the favorable response of the cardiac nervous system to the combined treatment: carvedilol has the nonselective beta-blocking action and amiodarone has a beta-blocking action, an antifibrillatory effect, a cardioprotective effect through thyroid hormone metabolism, and an antioxidant action. Moreover, amiodarone weakly inhibits carvedilol metabolism so its action may increase.

Pimobendan is a calcium sensitizer that shows both inotropic and peripheral vasodilating effects. Since the intracellular calcium concentration is decreased in the failing myocardium, pimobendan is expected to be beneficial in the treatment of HF. Takeda et al[70] demonstrated that, 12 months after treatment with pimobendan, H/M ratio on MIBG scintigraphy was significantly increased in patients with HF, suggesting that this drug was effective on cardiac sympathetic function in patients with HF.

To date, studies evaluating the efficacy of renin inhibitors such as aliskiren through MIBG scintigraphy are lacking in the literature; original studies addressing this issue are expected.

Conclusions

This review underlines the clinical usefulness of myocardial ^{123}I-MIBG scintigraphy in patients with HF. This innervation imaging method can be successfully used to assess changes in cardiac sympathetic neuronal function caused by several pharmacological interventions in patients with HF. In the next future MIBG scintigraphy could potentially help guide treatment in a cost-effective manner.

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