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The Clinical Usefulness of Cardiac Sympathetic Nerve Imaging using ^{123}Iodine-Meta-iodobenzylguanidine Scintigraphy to Evaluate the Effectiveness of Pharmacological Treatments in Patients with Heart Failure

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Abstract

The autonomic nervous system plays an important role in the human heart. Activation of the cardiac sympathetic nerve system is a cardinal pathophysiological abnormality associated with the failing human heart. Myocardial imaging using ^{123}I-metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, has been applied to investigate the activity of the predominant neurotransmitter of the sympathetic nervous system. ^{123}I-MIBG uptake in the myocardium is known to be reduced after the onset of heart failure, and improves when heart failure is controlled; therefore, treatments for heart failure may be assessed based on improvements in ^{123}I-MIBG scintigraphic parameters. In this review, we summarized studies that have focused on the use of cardiac sympathetic nerve imaging using ^{123}I-MIBG scintigraphy to evaluate the effectiveness of pharmacological treatments in heart failure patients.

Keywords: Sympathetic nerve system, ^{123}I-MIBG scintigraphy, Heart failure
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Heart failure has a >20% mortality rate in the first year after its diagnosis and a 5-year mortality rate of approximately 50% (1). The cardiac sympathetic nervous system and renin-angiotensin-aldosterone-system (RAAS) are crucial compensatory mechanisms during heart failure (2). Activation of the sympathetic nervous system has been identified as one of the cardinal pathophysiological abnormalities associated with human heart failure (3). An enhanced sympathetic response is initially favorable because it compensates for decreased cardiac output. However, as heart failure progresses, this response leads to deleterious neurohormonal and myocardial structural changes that worsen the condition and increase the likelihood of arrhythmias and cardiac death (4).

The pharmacological treatment of heart failure involves neurohormonal antagonism, adrenergic blockade, and vasodilators. β-adrenergic blocking agents, such as bisoprolol, metoprolol, and carvedilol, have been shown to improve left ventricular (LV) function and increase the transplant-free survival rate in heart failure patients (5-7).

Angiotensin-converting enzyme (ACE) inhibitors decrease afterload and increase cardiac output, which improves the survival of heart failure patients (8,9). However, ACE inhibitors do not fully suppress the production of angiotensin II (10). Therefore, non-ACE-mediated enzymatic pathways are important in the conversion of angiotensin I to angiotensin II (11). Angiotensin II receptor blockers (ARBs) may exert

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more complete angiotensin II blockade than ACE inhibitors by inhibiting angiotensin II binding at the receptor level; therefore, they may reduce heart failure-associated mortality and morbidity（12,13）.

Aldosterone promotes the retention of sodium, loss of magnesium and potassium, myocardial and vascular fibrosis, structural remodeling, and sympathetic activation（14）. Treatments that block aldosterone receptors have been reported to reduce mortality and morbidity in heart failure patients（15,16）.

Amiodarone exerts both β- and potassium channel blocker-like actions（17）. This improvement is multifaceted, including antiarrhythmic and antifibrillatory effects, the ability to prolong action potentials via changes in potassium transport, and the noncompetitive inhibition of α-adrenergic receptors（18）.

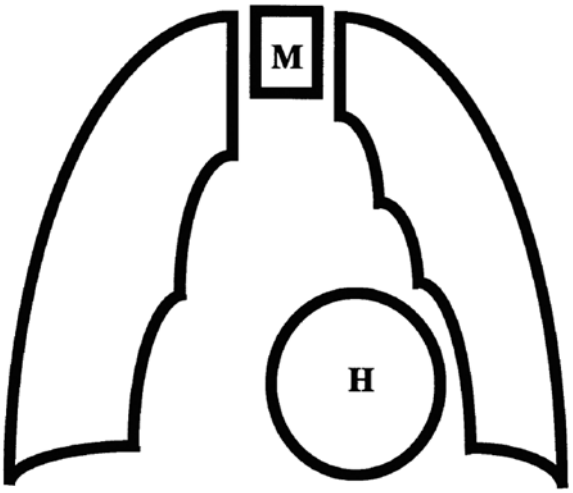

Fig. 1 Cardiac ^{123}I-meta-iodobenzylguanidine uptake was quantified as the H/M ratio, using regions of interest positioned over the heart（H）and upper mediastinum（M）.

Cardiac sympathetic nerve imaging with ^{123}I-MIBG

Myocardial imaging with ^{123}I-metaiodobenzylguanidine（MIBG）, an analog of norepinephrine（NE）, is a useful tool for detecting abnormalities in the myocardial adrenergic nervous system in heart failure patients（19,20）. A relationship has been reported between myocardial NE and ^{123}I-MIBG myocardial uptake in heart failure patients（19）; therefore, cardiac sympathetic nerve activity（CSNA）, evaluated by ^{123}I-MIBG scintigraphy, is a useful prognostic tool for heart failure（20-23）.

The cellular mechanism of MIBG uptake and storage in pre-synaptic vesicles is identical to that of NE. MIBG and NE share two uptake systems: specific（type-1 or uptake-1）and non-specific（type-2）, using passive diffusion（24）. Type-1 uptake is an active process catalyzed by a temperature- and Na-dependent membrane carrier protein with high affinity and low capacity, which is oxygen-dependent and desipramine- and cocaine-sensitive（25）. Type-2 uptake is temperature-dependent, but Na- and oxygen-independent. In addition, it is nonsaturable up to 5 mM MIBG（24）. At low concentrations, MIBG is primarily taken up *via* the type-1 mechanism. However, the type-2 mechanism is predominant at high concentrations, for example with ^{131}I-MIBG. After diffusing through the cell membrane, the tracer is taken up by neurosecretory vesicles *via* an active transport mechanism（26）.

In the scintigraphic method of cardiac sympathetic nerve imaging, ^{123}I-MIBG is intravenously administered at rest and early（after 10-30 minutes）and delayed（after 3-4 hours）images are then obtained. Planar images with an anterior view are sufficient for evaluating cardiac sympathetic function. Single-photon emission computed tomography（SPECT）images are often acquired to evaluate regional myocardial uptake patterns（27）. The common semi-quantitative indices used for the interpretation of cardiac sympathetic nerve images are the heart-to-mediastinum ratio（H/M）and washout rate（WR）. The H/M ratio is determined from anterior planar delayed ^{123}I-MIBG images（Fig. 1）. The WR is calculated using the following formula（19）: {([H]-[M]) early-([H]-[M]) delayed}/([H]-[M]) earlyX100（%）, where [H] = mean count/pixel in the left ventricle and [M] = mean count/pixel in the upper mediastinum. The delayed H/M ratio and WR represent myocardial NE content（i.e., intravesicular NE concentration）and presynaptic NE kinetics at the myocardial sympathetic nerve endings, respectively（19）.

Pharmacological treatments and ^{123}I-MIBG imaging

1）β-Blockers

Several trials previously demonstrated an improvement in CSNA, assessed by ^{123}I-MIBG scintigraphy, after β-blocker treatments in heart failure patients. Early trials were conducted to detect changes in CSNA after the administration of metoprolol. Fukuoka et al.（28）evaluated 13 patients with dilated cardiomyopathy（DCM）before and after these treatments. The LV ejection fraction（LVEF）improved by ≥5% in 7 patients, but not in 6 patients. The regional WR was calculated from ^{123}I-MIBG SPECT images before, 1 month, and 3 months following the treatments. This parameter significantly decreased in the improvement group, but not in the non-improvement group. Kakuchi et al.（29）examined DCM patients divided into groups

A and B based on those who did and did not reach a daily dose of >20 mg metoprolol by 3 months. The baseline WR in group A was lower than that in group B. After 1 month, the delayed H/M ratio increased in group A, but not in group B. Moreover, de Milliano et al.（30）examined 58 patients with heart failure who were randomized to a maximal tolerable dose of metoprolol or placebo, and found a 21.9% increase in ^{123}I-MIBG uptake after 6 months, whereas the placebo group showed a 7.8% decrease.

The third-generation β-blocker, carvedilol, has been shown to reduce morbidity and mortality in heart failure patients（7）. Fujimura et al.（31）divided 42 DCM patients into 2 groups: 27 responders and 15 non-responders with an LVEF increase of >5% and ≤5%, respectively. In the responder group, the delayed H/M significantly increased（1.91±0.34 to 2.24±0.53, p<0.01）and WR decreased（49%±11% to 39%±9%, p<0.01）after the treatment. In contrast, no significant changes were observed in the non-responder group. Agostini et al.（32）examined the effects of carvedilol on CSNA in 22 patients with DCM（LVEF <40%）. After the treatment, the delayed H/M ratio increased（1.45±0.23 to 1.70±0.25; p=0.0001）, thereby confirming that carvedilol improved CSNA in DCM patients.

Yamazaki et al.（33）assessed 58 patients with DCM and found a correlation between LVEF and ^{123}I-MIBG scintigraphic parameters（extent and severity score, and WR from SPECT imaging）obtained before and after treatments（nipradilol, metoprolol, or carvedilol）. Patients were divided into groups A and B, showing a >10% and <10% improvement in LVEF, respectively. ^{123}I-MIBG parameters improved after the β-blocker treatment in group A, whereas no change occurred in group B. In addition, the high uptake of early ^{123}I-MIBG images predicted an improvement in LVEF after β-blocker therapy. The same investigation by Fujimoto et al.（34）showed the utility of cardiac ^{123}I-MIBG imaging to predict cardiac events in 53 patients with DCM. There were no cardiac events in DCM patients with an improvement in WR of ≥10% after the β-blocker treatments.

Hirooka et al.（35）reported that carvedilol was preferable to metoprolol in heart failure patients. Drug intolerance was noted in 24% of patients in the metoprolol group（7/29）and 19% of patients in the carvedilol group（10/62）. This study confirmed that metoprolol and carvedilol, when tolerated, both improved CSNA and cardiac function. Toyama et al.（36）subsequently compared two groups of 15 patients with DCM who were receiving either carvedilol or metoprolol. In both groups, the delayed H/M significantly increased（carvedilol: 1.67±0.31 to 2.01±0.36, p<0.01; metoprolol: 1.68±0.21 to 1.93±0.32, p<0.01）, and WR decreased（carvedilol: 47%±15% to 36%±16%, p<0.01; metoprolol: 51%±10% to 37%±11%, p<0.01）after treatments. These findings revealed that the carvedilol treatment improved CSNA to a similar degree as metoprolol.

Gerson et al.（37）reported that a carvedilol treatment improved CSNA in 22 patients with idiopathic cardiomyopathy. Patients with advanced impairments in CSNA, manifested with the delayed H/M ratio of <1.40, showed significant improvements with carvedilol（1.26±0.12 to 1.39±0.20, p=0.004）. A similar study by Lotze et al.（38）showed an improvement in ^{123}I-MIBG imaging after treatments with various β-blockers（metoprolol, carvedilol, and bisoprolol）in DCM patients.

A randomized, multicenter, double-blind, placebo-controlled study of carvedilol was conducted by Cohen-Solal et al.（39）in heart failure patients. ^{123}I-MIBG scintigraphic parameters improved after 6 months of the treatment with carvedilol, but remained unchanged in the placebo group. Chizzola et al.（40）showed that CSNA gradually improved, as indicated by improved H/M ratios, when carvedilol was added to the standard treatment for DCM patients than when a placebo was added. In the late 2000s, Kasama et al.（41）studied the influence of carvedilol on CSNA and LV remodeling in 30 patients with DCM. ^{123}I-MIBG scintigraphic and echocardiographic parameters significantly improved after 12 months. Moreover, a correlation was noted between changes in the delayed total defect score, H/M ratio, and WR and those in the LV end-diastolic volume（EDV）（Fig. 2）and end-systolic volume（ESV）（Fig. 3）after the treatment. They concluded that carvedilol not only improved CSNA, but also prevented LV remodeling. Toyama et al.（42）compared the effects of the β-blocker metoprolol and ACE inhibitor enalapril in 24 patients with DCM. Although the delayed H/M was increased in both groups（metoprolol: 1.87±0.31 to 2.14±0.29; p<0.01; enalapril: 1.82±0.28 to 1.94±0.26; p<0.05）, the extent of the change after the metoprolol treatment was greater than that after enalapril（p<0.05）.

Two previous studies reported that β-blockers were not beneficial for CSNA by ^{123}I-MIBG scintigraphy. These studies assessed bucindolol（43）and carvedilol（44）treatments. The most likely reason for these results was the relatively short-term and low-dose β-

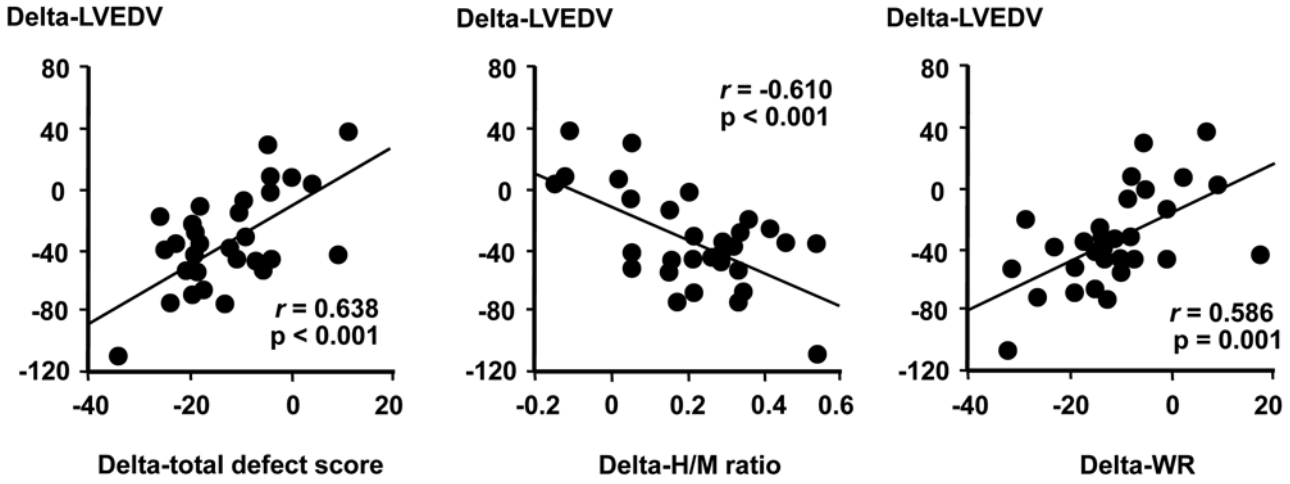

Fig. 2 Correlations between changes in ^{123}I-MIBG scintigraphic findings and left ventricular end-diastolic volume（LVEDV）after the carvedilol treatment in 30 patients with dilated cardiomyopathy. Delta-(*X*) = [(*X*) value after treatments]-[baseline value of (*X*)], where (*X*) = ^{123}I-MIBG scintigraphic or echocardiographic parameters.

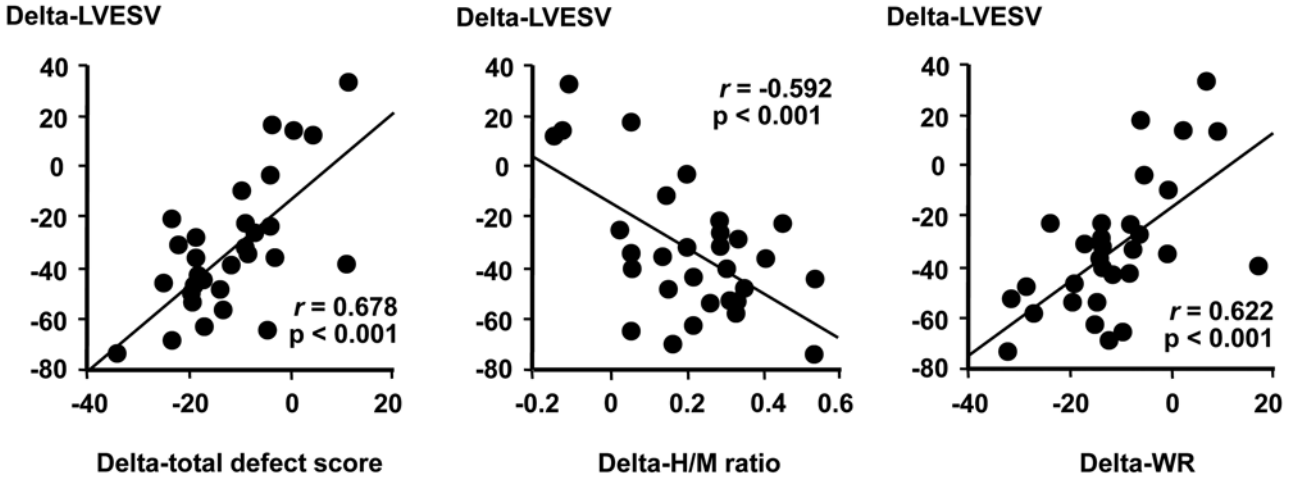

Fig. 3 Correlations between changes in ^{123}I-MIBG scintigraphic findings and left ventricular end-systolic volume（LVESV）after the carvedilol treatment in 30 patients with dilated cardiomyopathy. Delta-(*X*) = [(*X*) value after treatments]-[baseline value of (*X*)], where (*X*) = ^{123}I-MIBG scintigraphic or echocardiographic parameters.

blocker treatments used when compared with other studies.

2）ACE inhibitors

A previous study reported that the activation of the RAAS enhanced NE release（45）and prevented its uptake（46）in the myocardium; therefore, the inhibition of the RAAS may improve CSNA. Somsen et al.（47）evaluated 23 patients with heart failure（LVEF ＜40%), and found that ^{123}I-MIBG uptake significantly increased（$p<0.02$）after a 6-week treatment with enalapril. However, ^{123}I-MIBG uptake was not related to plasma NE. These results provided some evidence for the hypothesis that the restoration of cardiac sympathetic neuronal uptake was a beneficial effect of enalapril. These findings were confirmed by Takeishi et al.（48）using a common method of analysis for ^{123}I-MIBG planar imaging. They investigated 29 patients receiving conventional heart failure treatments. Nineteen patients additionally received enalapril while 10 patients were treated conventionally. In the enalapril group, early and delayed H/M ratios both increased（1.60±0.22 to 1.73±0.28, $p<0.05$; 1.63±0.28 to 1.82±0.33, $p<0.01$, respectively）and WR decreased（38%±11% to 30%±12%, $p<0.01$）. However, these parameters were not significantly changed in the conventional treatment group. In addition, Soeki et al.（49）reported that early and delayed H/M ratios both significantly increased（1.99±0.38 to 2.20±0.50, $p<0.05$; 1.86±0.44 to 2.09±0.51, $p<0.05$, respectively）after the treatment of heart failure with enalapril.

Perindopril has been shown to more strongly inhibit

the RAAS in the failing heart than enalapril (50); therefore, it may induce a greater improvement in CSNA. Kasama et al. (51) randomly assigned 40 patients with heart failure (LVEF <45%) to a perindopril (n=20) or enalapril (n=20) group. Six months after the treatment with perindopril, the delayed H/M ratio increased (1.62±0.27 to 1.76±0.29, p<0.01) and WR decreased (50%±14% to 42%±14%, p<0.05). In contrast, no significant differences were observed in patients receiving enalapril. A similar comparative study was conducted by Tsutamoto et al. (52). Forty-five heart failure patients undergoing conventional treatments, including enalapril, were randomized into 2 groups; enalapril switched to perindopril group (n=21) and a continuous enalapril treatment group (n=24). In the perindopril group, the delayed H/M ratio significantly increased (2.00±0.07 to 2.15±0.07, p=0.013) and WR decreased (33.0%±1.4% to 30.5%±1.2%, p=0.03) after 6 months. Conversely, no significant changes were noted in the enalapril group. These findings (51,52) suggested that perindopril was superior to enalapril and exerted more favorable effects on CSNA, in addition to improved cardiovascular outcomes.

3) Angiotensin II receptor blockers (ARBs)

Shinohara et al. (53) published the first study investigating the effects of ARBs on CSNA in heart failure patients. They examined 34 patients with a fractional shortening of the LV diameter ≤25% or LVEF ≤45%, treated with losartan or candesartan. Although no significant difference was observed in the delayed H/M ratio, the WR significantly decreased (32.6%±7.6% to 28.2%±7.5%; p<0.001) after 6 months.

Thereafter, ARBs were clearly shown to improve CSNA in patients with heart failure when these drugs were administered with ACE inhibitors. Kasama et al. (54) studied 32 patients with heart failure treated with an ACE inhibitor. Patients were randomized to additionally receive valsartan (group A) or continue with their current regimen (group B). The delayed H/M ratio significantly increased (1.66±0.23 to 1.81±0.23; p<0.001) and WR decreased (47%±9% to 39%±10%; p<0.01) after 6 months in group A. In contrast, no significant changes were noted in group B. Furthermore, ARBs were suggested to improve the condition of patients with heart failure and preserve LVEF. Kasama et al. (55) selected 50 patients with non-ischemic heart failure and preserved LVEF (>40%) who were treated with standard treatments. Patients were randomly selected to receive candesartan (n=25) or placebo (n=25). ^{123}I-MIBG scintigraphic parameters in the candesartan group significantly improved after 6 months, whereas no significant changes were observed in the placebo group. These findings suggested that the addition of candesartan to an ACE inhibitor resulted in the stronger inhibition of RAAS and an increase in the myocardial uptake of NE in heart failure patients with preserved LVEF.

The same investigators showed that ARB induced a greater improvement in CSNA than an ACE inhibitor (56). They examined 50 patients with heart failure (LVEF <40%) who were randomly assigned to receive valsartan (n=25) or enalapril (n=25). The delayed H/M ratio increased (1.70±0.17 to 1.78±0.22; p<0.05) and WR decreased (46%±11% to 41%±10%; p<0.05) after a 6-month treatment with valsartan. In contrast, no significant differences were noted after the enalapril treatment.

4) Aldosterone blockers (mineralocorticoid receptor antagonists)

Aldosterone has been shown to prevent the uptake of NE in the myocardium (46); therefore, several trials were designed to assess improvements in CSNA in patients with heart failure who were being chronically treated with aldosterone receptor blockers. Barr et al. (57) demonstrated that myocardial ^{123}I-MIBG uptake increased more in heart failure patients treated with spironolactone than with a placebo.

Kasama et al. (58) investigated the effects of spironolactone on CSNA using ^{123}I-MIBG scintigraphy. Thirty patients with heart failure (LVEF <40%) treated with standard conventional therapies were divided into 2 groups: 15 patients received spironolactone (group A) and 15 patients continued their current regimen (group B). The delayed H/M ratio increased (1.62±0.20 to 1.83±0.27; p<0.0001), and WR decreased (51%±9% to 40%±15%; p<0.001) after 6 months in group A. These parameters did not significantly change in group B. These findings were confirmed in a subsequent study by the same investigators (59). They assessed 30 patients with DCM who were randomly assigned to a spironolactone or conventional treatment, and found that the delayed H/M ratio increased (1.64±0.20 to 1.86±0.27; p<0.0001) and WR decreased (55%±12% to 41%±15%; p<0.0005) in the spironolactone only group. Therefore, they concluded that the addition of spironolactone to standard therapy may be more effective for non-ischemic cardiomyopathy than for ischemic cardiomyopathy.

Previous studies (57-59) included a relatively small number of patients; therefore, Kasama et al. (60)

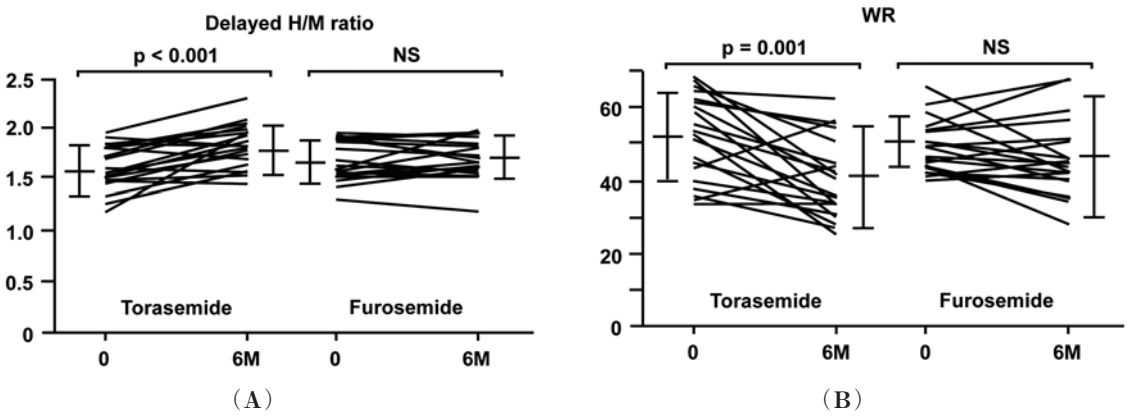

Fig. 4 Comparison of cardiac ^{123}I-meta-iodobenzylguanidine scintigraphic findings for the delayed H/M ratio（A）and WR（B）during the treatment in the torasemide and furosemide groups. 6M=after 6 months of therapy.

progressed to evaluating the effects of spironolactone in 208 patients with heart failure（LVEF ＜40%）. All patients were identified on the basis of a history of decompensated acute heart failure requiring hospitalization. These patients underwent ^{123}I-MIBG scintigraphy and echocardiography immediately before discharge and after 6 months. The patients were retrospectively divided into spironolactone（n＝82）and non-spironolactone（n＝126）groups. All parameters improved in both groups. However, the extent of changes in the delayed H/M ratio and WR was greater in the spironolactone group than in the non-spironolactone group（all, p＜0.001）.

The same group focused their attention on the effects of a combined treatment with spironolactone and candesartan on CSNA compared with candesartan alone（61）. Fifty patients with heart failure（LVEF ＜45%）were randomly assigned to a candesartan plus spironolactone（group A; n＝25）or to candesartan alone（group B; n＝25）group. After 6 months, all MIBG scintigraphic parameters had improved in both groups. However, the degree of changes in these parameters was significantly better in group A than in group B.

5）Diuretics

Loop diuretic treatments activate the RAAS and CSNA and may lead to poor prognoses in heart failure（62）. However, the long-acting loop diuretic, azosemide, has been shown to have a milder effect on the RAAS and CSNA than the short-acting loop diuretic, furosemide（62）. A comparative study of azosemide and furosemide was undertaken by Hisatake et al.（63）and performed using a crossover design: two groups of 11 patients with heart failure were randomized to either azosemide or furosemide. The treatments were administered for 6 months and patients were then transferred over to the second treatment. The delayed H/M ratio（p＝0.011）was significantly higher, while the WR was significantly lower（p＜0.0001）after the final administration in the azosemide group than in the furosemide group.

Moreover, torasemide, another loop diuretic, was previously reported to inhibit the RAAS and exhibited anti-aldosteronergic properties in pharmacological studies（64）. Kasama et al.（65）compared the effects of torasemide and furosemide. Forty patients with non-ischemic heart failure（LVEF ＜45%）were randomly assigned to a torasemide（n＝20）or furosemide（n＝20）group. The delayed H/M ratio increased（1.61±0.19 to 1.77±0.24; p＜0.001）（Fig. 4A）and WR decreased（52%±12% to 41%±14%; p＝0.001）（Fig. 4B）after 6 months in patients receiving torasemide. In contrast, no significant changes were observed in patients receiving furosemide.

6）Other drugs

Toyama et al.（66）investigated whether amiodarone exerted some effects on CSNA in patients with heart failure. They compared 15 patients with DCM receiving amiodarone and 15 receiving the β-blocker metoprolol. MIBG scintigraphic parameters improved in both groups 1 year after these treatments, suggesting that the amiodarone treatment improved CSNA to a similar degree as metoprolol. The same group（67）reported that a combined treatment with carvedilol and amiodarone significantly improved ^{123}I-MIBG scintigraphic parameters more than carvedilol alone.

Pimobendan is a calcium sensitizer with inotropic and peripheral vasodilating effects. Intracellular calcium concentrations are decreased in the failing myocardium. Takeda et al.（68）demonstrated that the delayed H/M

ratio was significantly increased after a 12-months treatment with pimobendan, suggesting that it may improve CSNA in heart failure.

CSNA is modulated by the activation of adenosine triphosphate-sensitive potassium（K-ATP）channels（69）; therefore, Kasama et al.（70）determined whether the K-ATP channel opener, nicorandil, improved CSNA in heart failure patients. Using their database（23）, they employed propensity score matching（PSM）to compare patients who had received nicorandil（n＝85）and those who did not（n＝85）. After 6 months, greater improvements were observed in ^{123}I-MIBG scintigraphic parameters in the nicorandil group than in the non-nicorandil group, confirming that nicorandil improved CSNA in heart failure patients. The same investigators focused on the K-ATP channel opening activity of 3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitors（statins）. Sano et al.（71）also used PSM to compare patients who did（n＝82）and did not（n＝82）receive statins. Greater improvements were noted in ^{123}I-MIBG scintigraphic parameters in the statin group than in the non-statin group.

Few studies have evaluated the efficacy of renin inhibitors（such as aliskiren）or angiotensin receptor-neprilysin inhibitors（ARNi）using ^{123}I-MIBG scintigraphy; therefore, studies to examine these treatments need to be conducted in the future.

Summary of the clinical usefulness of ^{123}I-MIBG scintigraphy for heart failure

Since heart failure patients have a high mortality rate（1）, clinical management is important to prevent cardiac death. LV dysfunction and LV dilatation have been identified as prognostic indicators for patients with heart failure（10）. On the other hand, ^{123}I-MIBG scintigraphy was shown to be a more useful predictor than these LV parameters（23）. Plasma BNP concentrations also have prognostic value in these patients（72）. However, the combination of ^{123}I-MIBG scintigraphy and BNP concentrations provides a more incremental prognostic value than BNP alone（73）. Furthermore, the prediction formula and nomograms using ^{123}I-MIBG scintigraphy may be used for the risk stratification of heart failure patients（74）. Accordingly, we propose to use this imaging modality to evaluate the severity of heart failure, responses to therapy, and prognoses.

Study limitations

Quantitative ^{123}I-MIBG parameters differ between institutions and instruments because the choice of collimator influences the H/M ratio and WR value; therefore, cardiac ^{123}I-MIBG has yet to achieve broad clinical acceptance. Few multicenter trials using this imaging modality have been conducted. However, a correction method to standardize the ^{123}I-MIBG imaging among various gamma cameras and collimators has been reported（75）. The clinical usefulness of ^{123}I-MIBG scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with heart failure needs to be determined using a prospective, multi-center trial with larger numbers of patients in the future.

Conclusions

This review underlines the clinical usefulness of myocardial ^{123}I-MIBG scintigraphy in patients with heart failure. This cardiac sympathetic nerve imaging method may be successfully used to assess the changes in CSNA caused by many pharmacological interventions in patients with heart failure.

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Conflicts of Interest

None

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