# Effects of Statin Therapy on Cardiac Sympathetic Nerve Activity and Left Ventricular Remodeling in Patients With Chronic Heart Failure

## A Propensity Score-Matched Analysis

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**Abstract:** Statin therapy reduces enhanced cardiac sympathetic nerve activity (CSNA) in patients with heart disease, and prevents left ventricular (LV) remodeling in chronic heart failure (CHF) patients. We sought to evaluate the effects of statin therapy on CSNA, as evaluated by ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, and LV remodeling in CHF patients.

This study was sub-analysis of our previous report of the result that the serial ^{123}I-MIBG studies were the most useful prognostic indicator in CHF patients. Patients with CHF (n = 208; left ventricular ejection fraction <45%) but no cardiac events for at least 5 months before the study, were identified according to their history of decompensated acute heart failure requiring hospitalization. The patients underwent ^{123}I-MIBG scintigraphy and echocardiography immediately before hospital discharge and after 6 months. The delayed % denervation, delayed heart/mediastinum count (H/M) ratio, and washout rate (WR) were determined by ^{123}I-MIBG scintigraphy. The LV end-diastolic volume (EDV) and end-systolic volume (ESV) were also determined by echocardiography. We selected 164 patients and used propensity score matching to compare patients who received oral statin (n = 82), and those who did not (n = 82).

The changes in ^{123}I-MIBG scintigraphic parameters improved, and in echocardiographic LVEDV and LVESV reduced in the statin group compared with those in the non-statin group. Moreover, there were significant correlations between changes in the ^{123}I-MIBG scintigraphic findings and those in the LVEDV (% denervation, $r = 0.534$, $P < 0.001$; H/M ratio, $r = -0.516$, $P < 0.001$; and WR, $r = 0.558$, $P < 0.001$); or the LVESV (% denervation, $r = 0.479$, $P < 0.001$; H/M ratio, $r = -0.450$, $P < 0.001$; and WR, $r = 0.520$, $P < 0.001$) in the statin group. In contrast, there was no relationship between these parameters in the non-statin group.

Statin therapy not only improved CSNA, but also reduced LV volume, in other wards, prevented LV remodeling in CHF patients.

**Abbreviations**: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CHF = chronic heart failure, CSNA = cardiac sympathetic nerve activity, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, H/M = heart/mediastinum count, LDL-C = low-density lipoprotein cholesterol, LV = left ventricular, MIBG = meta-iodobenzylguanidine, SPECT = single photon emission computed tomography, TDS = total defect score, WR = washout rate.

## INTRODUCTION

The 3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduce mortality and morbidity in various patients, including those with dyslipidemia, ischemic heart disease, and cerebrovascular disease.[1–3] Statins effectively lower low-density lipoprotein cholesterol (LDL-C) level; in addition, statins have other potentially favorable "pleotropic" effects in patients with chronic heart failure (CHF).[4,5]

Activation of the cardiac sympathetic nerve activity (CSNA) is a cardinal pathophysiological abnormality associated with human heart failure.[6] Therefore, plasma norepinephrine concentrations affect the prognosis of CHF patients.[7] Myocardial imaging with ^{123}I-metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, is useful for detecting abnormalities in the myocardial adrenergic nervous system in CHF patients.[8,9] Many studies have suggested that treatment of heart failure can improve CSNA, as evaluated by cardiac ^{123}I-MIBG scintigraphy.[10–23]

On the other hand, statin therapy reduces enhanced CSNA in patients with CHF.[5] Moreover, this agent is reported to prevent left ventricular (LV) remodeling in these patients.[24] Although favorable effects of statin therapy have been established, little is known about the effects of treatment with statin on cardiac ^{123}I-MIBG scintigraphic changes and LV parameters in patients with CHF.

Accordingly, this study was performed, using our previously reported data,[25] to determine whether statin therapy improves CSNA as evaluated by ^{123}I-MIBG scintigraphy, and whether this agent prevents LV remodeling in CHF patients.

## MATERIALS AND METHODS

### Study Patients and Protocol

From February 2000 through August 2005, 459 patients were admitted to our institution with their first episode of

decompensated acute heart failure with a LV ejection fraction (EF) of less than 45%, according to the inclusion criteria described in our previous study.[25] This study was sub-analysis using our previous database.[25] Chest radiography, standard electrocardiography, echocardiography were performed in all of the patients. In the acute phase, all patients were treated with standard heart failure treatment including intravenous diuretics, vasodilators (carperitide, nicorandil, nitroglycerin, and so on), and if necessary, dopamine or dobutamine was added to maintain the blood pressure. Patients were excluded from the study if they had unstable angina or recent acute myocardial infarction, and had performed any coronary revascularization procedures within 3 months (42 patients were excluded), and had primary hepatic failure, renal failure, or active cancer (29 patients). Moreover, patients with severe heart failure requiring mechanical support (intraaortic balloon pumping, left ventricular assist device, or cardiac resynchronization therapy) or patients requiring heart transplantation were also excluded (38 patients) (Figure 1).

During the stable period, the patients were treated with standard oral medications for heart failure, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-adrenergic blocking agents, and diuretics. None of the patients was treated with tricyclic antidepressants or other serotonin reuptake inhibitors. We performed ^{123}I-MIBG scintigraphy and echocardiography just before hospital discharge. However, 52 patients were excluded from this study because scintigraphy or echocardiography had not been performed during the hospitalization. The medical management of the patients was directed by an internist or cardiologist from our institution, and ^{123}I-MIBG scintigraphic and echocardiographic parameters were available to them. In this study, 18 patients were excluded because there were hard events (n = 10; cardiac events, n = 5; cerebral events, and n = 3; other events) for 5 months after enrollment.

The ^{123}I-MIBG scintigraphy and echocardiography were repeated about 6 months after hospital discharge (mean: 6.4 months). Patients were excluded from the study if the second evaluation had not been performed (30 patients), or if their medication changed between the first and the second evaluation (26 patients). The study was approved by the ethics review board of our institution, and informed written consent was obtained from all patients. Nine patients were excluded because informed consent was not obtained. Moreover, 7 patients were excluded because we lost to follow-up after second evaluation. We followed up 208 patients who had highly reliable information. The 208 study patients consisted of 130 men and 78 women with a mean age of 68.6 years (range 35–87 years).

To evaluate whether the statin treatment affected the CSNA and LV remodeling in our patients with CHF, we stratified our patients into statin (n = 82), and non-statin groups (n = 82), using propensity score matching (Figure 1). The statin agents included in this study were rosuvastatin (n = 22), atorvastatin (n = 20), fluvastatin (n = 16), pravastatin (n = 10), simvastatin (n = 9), and pitavastatin (n = 5). In addition, we did not select the statin treatment according to the clinical features in our CHF patients. For our study protocol,[25] statin was started during hospitalization, and this drug was continued follow-up period. Therefore, in other words, in the statin group, oral administration of statin was continued during the study period.

## ^{123}I-MIBG Scintigraphy

The ^{123}I-MIBG imaging method used has already been previously described.[25,26] In brief, the ^{123}I-MIBG was obtained from a commercial source (FUJIFILM RI Pharma Co. Ltd, Tokyo, Japan). At 15 minutes and 4 hours after injection, anterior planar and single photon emission computed tomographic (SPECT) images were obtained with a single-head gamma camera (Millennium MPR, GE Medical Systems, Waukesha, WI).

The heart/mediastinum count (H/M) ratio was determined from the anterior planar delayed ^{123}I-MIBG image using the standard method. The washout rate (WR) was calculated from early and delayed planar images. Regional tracer uptake was assessed semiquantitatively using a 5-point scoring system (0, normal to 4, no uptake) in 17 segments on the delayed SPECT image as recommended by the American Heart Association.[27] The total defect score (TDS) was calculated as the sum of all defect scores. The TDS was converted to the percentage of the total denervated myocardium (% denervation). The % denervation was calculated using the following formula: TDS/68 (maximum score = $4 \times 17$) × 100. At our laboratory, the reference range of the %denervation values is from 6 to 18; the delayed H/M ratio range from 2.18 to 2.70; and the normal WR range from 20% to 30%, as previously reported.[25,26]

## Echocardiography

Echocardiography was performed using standard methods. Two experienced independent echocardiography technicians who were blinded to the study methods performed all of the measurements. The LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and LVEF were calculated using the 2D-biplane method, as previously reported.[22]
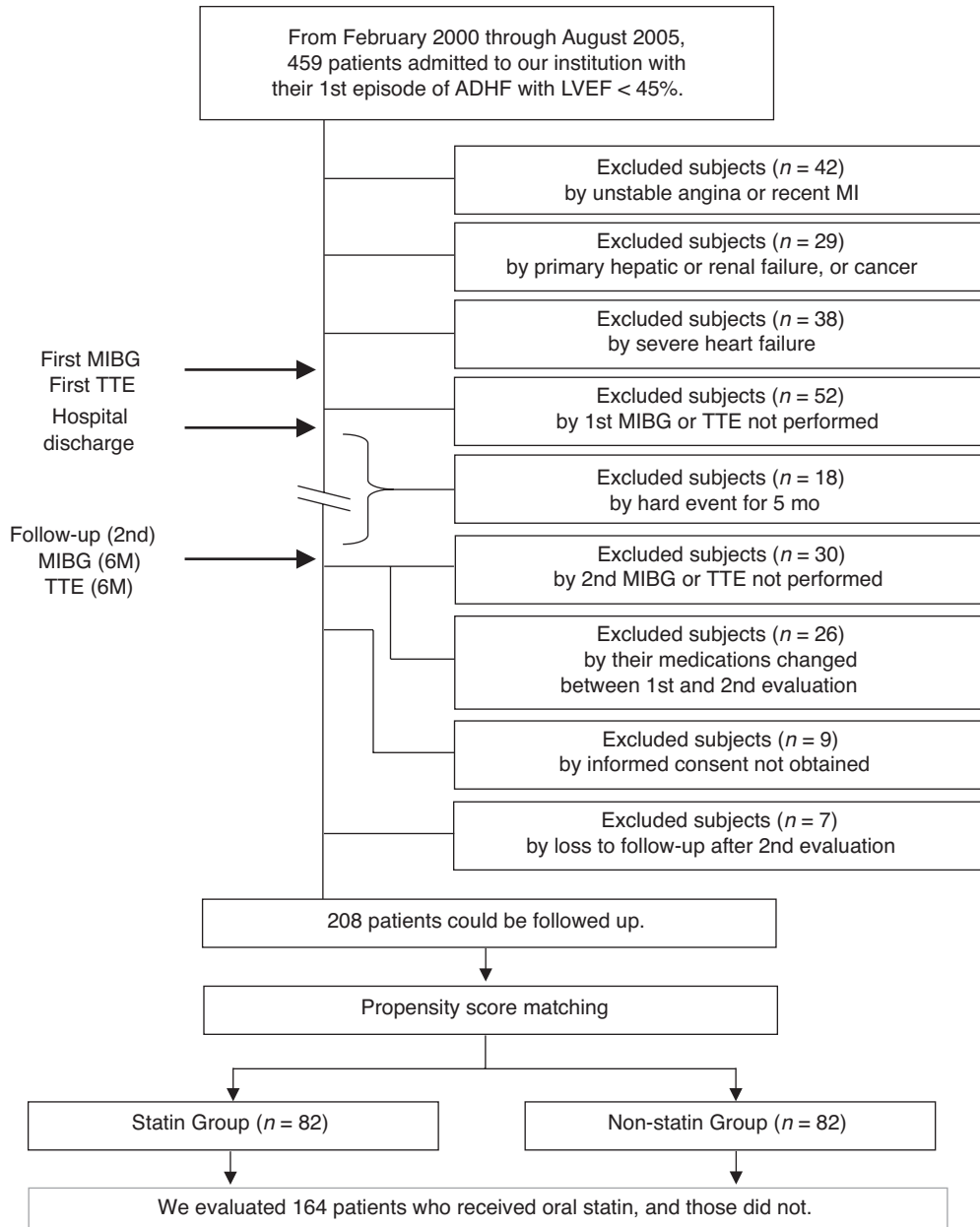
## Serial Changes Between the First and Second Scintigraphic and Echocardiographic Parameters

Changes between the first and second ^{123}I-MIBG scintigraphic (% denervation, H/M ratio, and WR) and echocardiographic parameters (EDV, ESV, and LVEF) were calculated using the following formula: delta − (X) = [(X) value after 6 months] − [baseline value of (X)], where (X) = ^{123}I-MIBG scintigraphic or echocardiographic parameters.

## Statistical Analysis

The analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, IL), or SAS version 9.1 (SAS Institute Inc, Cary, NC). Numerical results were expressed as the mean ± SD. In all the analyses, $P < 0.05$ was considered statistically significant. A propensity-matched analysis was conducted to minimize the selection bias for statin administration.[28] To obtain the propensity score for the probability that statin would be administered, multivariate logistic regression analyses were conducted. The propensity score was based on the following variables: age, sex, ischemic etiology, smoking, New York Heart Association (NYHA) functional classes, acute phase treatments, ^{123}I-MIBG scintigraphic and echocardiographic parameters, and presence of diabetes and hypertension. The patients in the statin and non-statin groups were matched 1:1 to 2 digits.

Categorical data were compared between the 2 groups using 2-sided chi-square tests, and differences between continuous variables were evaluated using the unpaired *t* test. NYHA functional classes were compared using the Wilcoxon matched pairs signed rank test. In patients who underwent a second assessment, changes from the baseline were evaluated within each treatment group using a paired *t* test and between the 2 groups using 2-way ANOVA. Linear regression analysis was performed to determine the relationship between continuous variables.

From February 2000 through August 2005, 459 patients admitted to our institution with their 1st episode of ADHF with LVEF < 45%.

Excluded subjects (*n* = 42) by unstable angina or recent MI

Excluded subjects (*n* = 29) by primary hepatic or renal failure, or cancer

Excluded subjects (*n* = 38) by severe heart failure

First MIBG
First TTE

Excluded subjects (*n* = 52) by 1st MIBG or TTE not performed

Hospital discharge

Excluded subjects (*n* = 18) by hard event for 5 mo

Follow-up (2nd)
MIBG (6M)
TTE (6M)

Excluded subjects (*n* = 30) by 2nd MIBG or TTE not performed

Excluded subjects (*n* = 26) by their medications changed between 1st and 2nd evaluation

Excluded subjects (*n* = 9) by informed consent not obtained

Excluded subjects (*n* = 7) by loss to follow-up after 2nd evaluation

208 patients could be followed up.

Propensity score matching

Statin Group (*n* = 82)

Non-statin Group (*n* = 82)

We evaluated 164 patients who received oral statin, and those did not.

**FIGURE 1.** Flow diagram of participants in current study. ADHF = acute decompensated heart failure, LVEF = left ventricular ejection fraction, MI = myocardial infarction, MIBG = metaiodobenzylguanidine scintigraphy, TTE = transthoracic echocardiography, 6 M = after 6 months of hospital discharge.

To evaluate the contribution of the degree of change in WR (ie, delta-WR), univariate and stepwise multivariate analyses were used to examine the variable of interest (Table 3). Moreover, in order to evaluate the effects of addition of statin to the beta-blocker on CSNA, each patients group treated with beta-blocker (n = 77), and treated without beta-blocker (n = 87) were evaluated by the same analysis (Tables 4 and 5, respectively).

## RESULTS

### Clinical Characteristics

No significant differences in clinical characteristics (except dyslipidemia) or cardiac medications were found

between the 2 groups. At baseline, the % denervation, H/M ratio, WR, LVEDV, LVESV, LVEF, NYHA functional class, and the frequency rates of follow-up LDL-C levels >100 mg/dL were similar between the 2 groups (Table 1).

### Comparison of Cardiac $^{123}$I-MIBG Scintigraphic Findings Before and 6 Months After Treatment

Figure 2 and Table 2 provide a summary of the % denervation, H/M ratios, and WR values. In both groups, % denervation was significantly decreased after 6 months relative to the baseline values. However, the delta-% denervation in the statin group was significantly lower than that in the non-statin

**TABLE 1.** Clinical Characteristics of the Patients

| | Statin (n = 82) | Non-statin (n = 82) | *P*-Value |
|---|---|---|---|
| Age (year) | 68 ± 11 | 69 ± 11 | 0.739 |
| Gender (male) | 50 (61%) | 51 (62%) | 0.872 |
| Ischemic etiology | 38 (46%) | 35 (43%) | 0.637 |
| Diabetes mellitus | 32 (39%) | 34 (41%) | 0.750 |
| Hypertension | 47 (57%) | 44 (54%) | 0.637 |
| Dyslipidemia (at the time of entry) | 66 (80%) | 30 (37%) | <0.001 |
| LDL-C >100 mg/dL (last follow-up data) | 23 (28%) | 29 (35%) | 0.314 |
| Current smoker | 27 (33%) | 24 (29%) | 0.613 |
| NYHA functional class | | | |
| II/III/IV | 28/40/14 | 25/47/10 | 0.601 |
| I-123 MIBG scintigraphy | | | |
| % denervation | 60.5 ± 10.2 | 58.1 ± 10.3 | 0.126 |
| H/M ratio | 1.64 ± 0.21 | 1.66 ± 0.20 | 0.506 |
| WR | 49.4 ± 11.2 | 47.9 ± 9.6 | 0.379 |
| Echocardiography | | | |
| LVEDV (mL) | 182 ± 45 | 181 ± 39 | 0.866 |
| LVESV (mL) | 124 ± 38 | 123 ± 40 | 0.901 |
| LVEF(%) | 33 ± 7 | 33 ± 8 | 0.743 |
| Medical treatment | | | |
| Other lipid-lowering drugs | 24 (29%) | 30 (37%) | 0.319 |
| ACE inhibitor | 57 (66%) | 54 (68%) | 0.616 |
| ARB | 51 (62%) | 54 (65%) | 0.625 |
| Beta-blocker | 40 (51%) | 37 (45%) | 0.638 |
| Digitalis | 13 (16%) | 16 (20%) | 0.539 |
| Diuretics | 76 (93%) | 76 (93%) | 1.000 |

Values are mean ± SD or number (%).

ACE = angiotensin-converting enzyme, ARB = angiotensin-receptor blocker, H/M = heart/mediastinum count, LDL-C = low-density lipoprotein cholesterol, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVSDV = left ventricular end-systolic volume, MIBG = meta-iodobenzylguanidine, NYHA = New York Heart Association, WR = washout rate.

group. In both groups, the H/M ratios were significantly increased after 6 months compared with the baseline values. However, the delta-H/M ratios were significantly higher in the statin group than those in the non-statin group. Finally, the WR in the statin group was significantly decreased after 6 months relative to the baseline values. In contrast, in the non-statin group, no significant differences were observed between the baseline and 6 months posttreatment values. Moreover, delta-WR was significantly lower in the statin group than in the non-statin group.

## Comparison of Echocardiographic Findings Before and 6 Months After Treatment

Table 2 also provides a summary of the LVEDV, LVESV, and LVEF. In both groups, LVEDV and LVESV were significantly decreased and LVEF was significantly increased after 6 months relative to the baseline values. The changes in LVEDV and LVESV were significantly greater in the statin group than those in the non-statin group. The change in LVEF in the statin group tended to be more favorable than that in the non-statin group, but these changes were not statistically significant.

## Relationship Between LV Volume and ^{123}I-MIBG Scintigraphic Findings Before and After Treatment

There were significant correlations between changes in the ^{123}I-MIBG scintigraphic findings and those in the LVEDV (% denervation, $r = 0.534$, $P < 0.001$; H/M ratio, $r = -0.516$, $P < 0.001$; and WR, $r = 0.558$, $P < 0.001$); or the LVESV (% denervation, $r = 0.479$, $P < 0.001$; H/M ratio, $r = -0.450$, $P < 0.001$; and WR, $r = 0.520$, $P < 0.001$) in the statin group (Figure 3). In contrast, there was no relationship between these parameters in the non-statin group.

## Evaluation of Factors Predicting Decreased Delta-WR

Table 3 shows the results of the univariate and multivariate analyses to assess factors predicting an increase in delta-WR. In the univariate analysis, age, non-beta-blocker treatment, and non-statin treatment were predictive factors. The stepwise multivariate analysis also identified age, non-beta-blocker treatment, and non-statin treatment as significant independent predictors of increasing delta-WR in the CHF patients.

In the patients treated with beta-blocker, in the univariate analysis, age and non-statin treatment were predictive factors. The stepwise multivariate analysis also identified age and non-statin treatment as significant independent predictors of increasing delta-WR (Table 4). In the patients treated without beta-blocker, in the univariate analysis, age, non-ACE inhibitor treatment, and non-statin treatment were predictive factors. The stepwise multivariate analysis identified age and non-statin treatment as significant independent predictors of increasing delta-WR (Table 5).
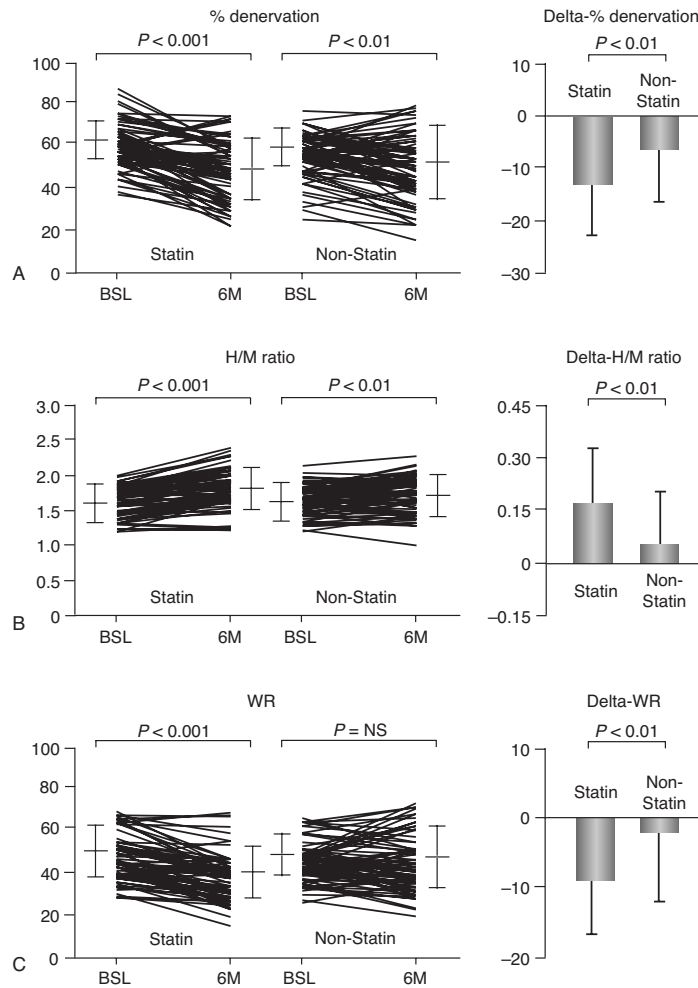
**FIGURE 2.** Comparison of cardiac $^{123}$I-metaiodobenzylguanidine scintigraphic findings for % denervation (A), H/M ratio (B), and WR (C) in the 2 groups. BSL = baseline. H/M = heart/mediastinum count. WR = washout rate. 6 M = after 6 months of therapy.

**TABLE 2.** Changes in % Denervation, Heart/Mediastinum Count Ratio, Washout Rate, Left Ventricular Volume, and Left Ventricular Ejection Fraction in Both Groups

| | **Statin** | | | **Non-statin** | | |
|---|---|---|---|---|---|---|
| | **Baseline** | **6 months** | **Delta** | **Baseline** | **6 months** | **Delta** |
| I-123 MIBG scintigraphy | | | | | | |
| % denervation | $60.5 \pm 10.2$ | $48.4 \pm 13.6^*$ | $-12.1 \pm 11.4$ | $58.1 \pm 10.3$ | $52.0 \pm 15.3^\dagger$ | $-6.1 \pm 12.0^\ddagger$ |
| H/M ratio | $1.64 \pm 0.21$ | $1.81 \pm 0.26^*$ | $0.17 \pm 0.15$ | $1.66 \pm 0.20$ | $1.74 \pm 0.24^\dagger$ | $0.08 \pm 0.16^\ddagger$ |
| WR | $49.4 \pm 11.2$ | $40.0 \pm 11.6^*$ | $-9.4 \pm 8.9$ | $47.9 \pm 9.6$ | $45.7 \pm 13.6$ | $-2.2 \pm 10.8^\ddagger$ |
| Echocardiography | | | | | | |
| LVEDV (mL) | $182 \pm 45$ | $159 \pm 49^*$ | $-23 \pm 31$ | $181 \pm 39$ | $167 \pm 40^\dagger$ | $-14 \pm 28^\S$ |
| LVESV (mL) | $124 \pm 38$ | $97 \pm 44^*$ | $-26 \pm 29$ | $123 \pm 40$ | $107 \pm 38^\dagger$ | $-16 \pm 23^\S$ |
| LVEF(%) | $33 \pm 7$ | $40 \pm 10^*$ | $8 \pm 8$ | $33 \pm 8$ | $38 \pm 9^\dagger$ | $5 \pm 5$ |

Values are means ± SD.

H/M = heart/mediastinum count, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVSDV = left ventricular end-systolic volume, MIBG = meta-iodobenzylguanidine, WR = washout rate.

[*] $P < 0.001$ vs baseline.
[†] $P < 0.01$ vs baseline.
[‡] $P < 0.01$ vs statin group.
[§] $P < 0.05$ vs statin group.
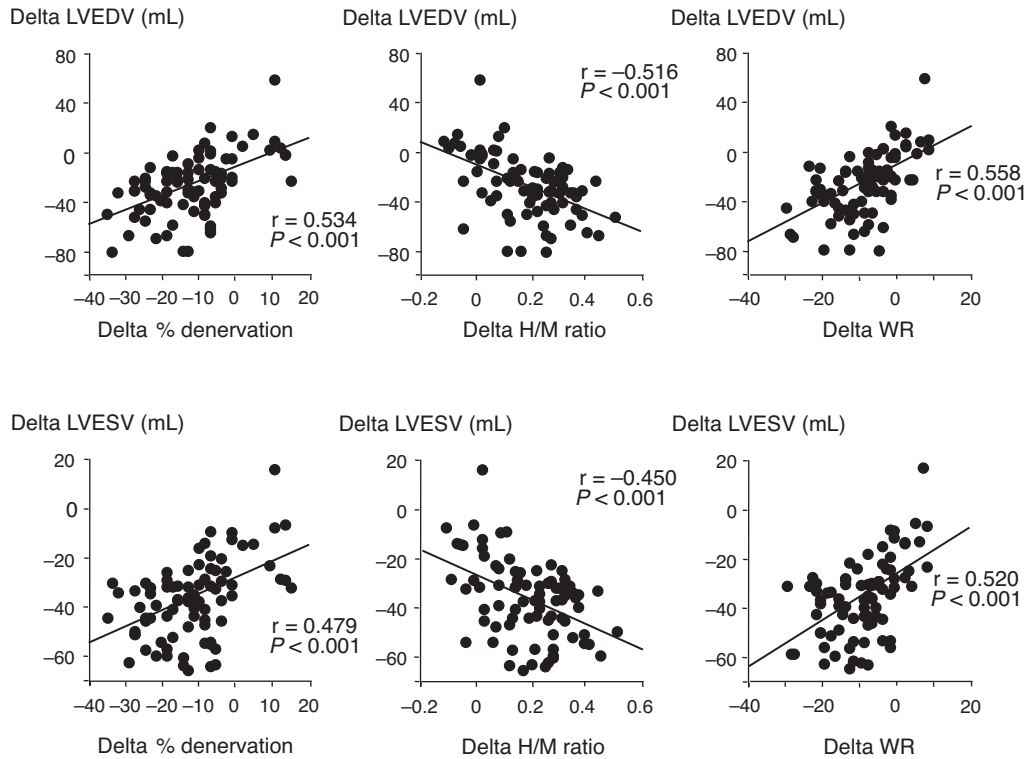
**FIGURE 3.** Correlations between the changes of ^{123}I-MIBG scintigraphic findings and left ventricular end-diastolic volume (LVEDV) (Top), or left ventricular end-systolic volume (LVESV) (Bottom) after statin therapy in patients with chronic heart failure. Delta LVEDV = the value of LVEDV after treatment − pretreatment value of LVEDV, Delta % denervation = the value of % denervation after treatment − pretreat-pretreatment value of % denervation, Delta H/M ratio = the value of H/M ratio after treatment − pretreatment value of H/M ratio, Delta WR = the value of WR after treatment − pretreatment value of WR, Delta LVESV = the value of LVESV after treatment − pretreatment value of LVESV. H/M ratio = heart/mediastinum count ratio, WR = washout rate.

## DISCUSSION

The patients were stratified into the statin and non-statin groups using propensity score matching. The ^{123}I-MIBG scintigraphic and echocardiographic parameters showed improvement in both groups, with more favorable changes in the statin group. There were significant correlations between changes in the ^{123}I-MIBG scintigraphic findings and LV volumes in the statin group. Moreover, stepwise multivariate analyses showed that non-statin treatment had an independent and significant negative relationship with delta-WR in CHF patients.

Inflammatory cytokines play an important role in the development and progression of CHF. They have been implicated in the development of LV remodeling, endothelial dysfunction, and increased cardiac myocyte apoptosis.[29] As statins

**TABLE 3.** Univariate and Multivariate Linear Model of Delta-WR

|  | Univariate | | Multivariate | |
| --- | --- | --- | --- | --- |
|  | Correlation coefficient | *P*-Value | Beta-coefficient | *P*-Value |
| Age | 0.234 | 0.003 | 0.206 | 0.003 |
| Gender (male = 1) | 0.131 | 0.096 | | |
| Ischemic etiology | 0.030 | 0.702 | | |
| NYHA | 0.023 | 0.769 | | |
| Digitalis | −0.102 | 0.183 | | |
| ACE inhibitor | −0.115 | 0.141 | | |
| Beta blocker | −0.404 | <0.001 | −0.372 | <0.001 |
| Statin | −0.293 | <0.001 | −0.236 | 0.001 |
| LVESV | 0.025 | 0.751 | | |
| LVEF | −0.029 | 0.710 | | |

ACE = angiotensin-converting enzyme, LVEF = left ventricular ejection fraction, LVSDV = left ventricular end-systolic volume, NYHA = New York Heart Association.

**TABLE 4.** Univariate and Multivariate Linear Model of Delta-WR in the Patients Treated With Beta-Blocker

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **Correlation coefficient** | **P-Value** | **Beta-coefficient** | **P-Value** |
| Age | 0.239 | 0.032 | 0.211 | 0.045 |
| Gender (male = 1) | 0.120 | 0.297 | | |
| Ischemic etiology | 0.111 | 0.335 | | |
| NYHA | 0.098 | 0.396 | | |
| Digitalis | −0.160 | 0.166 | | |
| ACE inhibitor | −0.158 | 0.182 | | |
| Statin | −0.402 | <0.001 | −0.404 | <0.001 |
| LVESV | 0.168 | 0.145 | | |
| LVEF | −0.180 | 0.117 | | |

ACE = angiotensin-converting enzyme, LVEF = left ventricular ejection fraction, LVSDV = left ventricular end-systolic volume, NYHA = New York Heart Association.

are well known to have anti-inflammatory effects and down-regulate inflammatory cytokines in failing heart,[30] it may attenuate LV global remodeling. In general, increasing of LV volume (ie, progression of LV remodeling) has been shown to be associated with the poor prognosis in patients with CHF.[31] Therefore, increasing effort has been directed toward pharmacological attenuation of LV volume for failing human hearts. Node et al[24] reported a significant reduction in LV volumes in patients with CHF after statin therapy compared with placebo. Similarly, in this study, LVEDV and LVESV were significantly decreased after the 6 months treatment in the statin group compared with the non-statin group. Therefore, our findings suggest that addition of statin to standard therapy can prevent LV remodeling in patients with CHF.

^{123}I-MIBG is an analogue of the adrenergic neuron-blocking agent guanethidine, which is thought to utilize the same myocardial uptake and release mechanisms as norepinephrine.[32] Therefore, cardiac ^{123}I-MIBG imaging is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in CHF patients.[8,9] Furthermore, many reports have suggested that the treatment of CHF with ACE inhibitors,[10–12] ARBs,[16–19] beta-blockers,[12–15] or spironolactone[19–22] can improve CSNA, based on cardiac ^{123}I-MIBG scintigraphic findings. However, little is known about the effects of statin therapy on CSNA in CHF patients. In this study, we examined whether statin therapy improved the ^{123}I-MIBG scintigraphic parameters in our CHF patients. We found that the statin group showed improvement compared with the non-statin group. Moreover, the stepwise multivariate analyses revealed that the non-statin treatment had an independent and significant relationship with increasing delta-WR in the CHF patients. Given our previously reported observation that delta-WR is the best currently available prognostic indicator for CHF,[25] our findings demonstrated for the first time that statin may be the available agent for improving CSNA and for preventing cardiac events of patients with CHF. Furthermore, both groups treated with and without beta-blocker, multivariate analyses revealed that the non-statin treatment had an independent and significant relationship with increasing delta-WR. Therefore, the statin treatment may reduce enhanced CSNA even if beta-blocker is not administrated.

It has been reported that the release of norepinephrine is enhanced, and uptake of norepinephrine is also prevented, in the failing heart.[33] Kang et al[34] demonstrated that the release and uptake of norepinephrine are modulated by activation of ATP-sensitive potassium channels in experimental rat models. As statin is reported to activate ATP-sensitive potassium channels and have also cardioprotective properties,[35] it may attenuate

**TABLE 5.** Univariate and Multivariate Linear Model of Delta-WR in the Patients Treated Without Beta-Blocker

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **Correlation coefficient** | **P-Value** | **Beta-coefficient** | **P-Value** |
| Age | 0.237 | 0.027 | 0.195 | 0.049 |
| Gender (male = 1) | 0.116 | 0.184 | | |
| Ischemic etiology | −0.058 | 0.592 | | |
| NYHA | 0.077 | 0.476 | | |
| Digitalis | −0.149 | 0.221 | | |
| ACE inhibitor | −0.265 | 0.013 | −0.189 | 0.062 |
| Statin | −0.381 | <0.001 | −0.345 | 0.001 |
| LVESV | 0.106 | 0.328 | | |
| LVEF | −0.117 | 0.280 | | |

ACE = angiotensin-converting enzyme, LVEF = left ventricular ejection fraction, LVSDV = left ventricular end-systolic volume, NYHA = New York Heart Association.

CSNA. Therefore, we hypothesize that statin therapy can improve CSNA in patients with CHF. However, further study will be required to confirm this hypothesis.

In this study, there were significant correlations between changes in the LV volume and the ^{123}I-MIBG scintigraphic parameters after treatment with statin in patients with CHF. However, no significant correlations were found in the non-statin group. With respect to the influence of statin, it is still unclear whether attenuation of LV volume, ie, due to the anti-remodeling effect of statin,[29] increases myocardial uptake of norepinephrine or whether increased myocardial uptake of norepinephrine leads to attenuation of LV volume. Therefore, further studies are necessary to clarify the relationship between the attenuation of LV volume and the increased myocardial uptake of norepinephrine.

Statins are classified either as hydrophilic (eg, rosuvastatin and pravastatin) and lipophilic (eg, atorvastatin, fluvastatin, simvastatin, and pitavastatin) according to the difference in their aqueous solubility. Differences in the pharmacologic properties of hydrophilic and lipophilic statins were identified in experimental[36] and clinical studies.[37] However, in the present study, no significant differences were found between the hydrophilic and lipophilic statin therapies in terms of changes in the ^{123}I-MIBG scintigraphic parameters. However, in the future, studies with a larger numbers of population should be conducted to examine the effects of statin on CSNA and to compare the effects of hydrophilic and lipophilic statins in CHF patients.

Currently, many independent reports from different centers around the world support the idea that ^{123}I-MIBG myocardial scintigraphy provides useful information for assessing patients with heart disease. The imaging modality appears valuable in predicting prognoses and estimating the efficacy of a therapy. However, quantitative ^{123}I-MIBG parameters differ between institutions and between instruments, and the tracer is not widely available. For these reasons, cardiac ^{123}I-MIBG has yet to achieve broad clinical acceptance; thus, few multicenter trials using the imaging modality have been conducted.[38–40] Therefore, the evidence supporting the clinical value of this imaging technique remains inadequate, requiring worldwide multicenter clinical trials involving larger numbers of patients to establish the efficacy of this imaging modality.

## CONCLUSIONS

The patients with CHF were divided into the statin group and the non-statin group by using propensity score matching. The ^{123}I-MIBG scintigraphic and echocardiographic parameters were improved in both groups but showed more favorable changes in the statin group. There were significant correlations between changes in the ^{123}I-MIBG scintigraphic findings and LV volumes in the statin group. These findings indicate that statin therapy can improve cardiac sympathetic nerve activity and prevent LV remodeling in patients with CHF.

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