ORIGINAL ARTICLE

Assessment of therapeutic effects of statin on cardiac sympathetic nerve activity after reperfusion therapy in patients with first ST-segment elevation myocardial infarction and normal low-density lipoprotein cholesterol

Shinya Takahashi, MD,[a] Shu Kasama, MD,[a,b] Takuji Toyama, MD,[a] Shota Suzuki, MPH,[b] Yukie Ito, CN,[b] Tomoaki Nakata, MD,[c] Masato Kasahara, MD,[b] and Masahiko Kurabayashi, MD[a]

[a] Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan
[b] Institute for Clinical and Translational Science, Nara Medical University Hospital, Kashihara, Nara, Japan
[c] Second Department of Internal Medicine (Cardiology), Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan

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Background. **Statin treatment reduces enhanced cardiac sympathetic nerve activity (CSNA) in patients with heart disease, and reduces adverse cardiac events in patients with coronary artery disease.**

Methods. **We retrospectively evaluated the first ST-segment elevation myocardial infarction (STEMI) patients and low-density lipoprotein cholesterol < 120 mg/dL in our database who underwent ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy 3 weeks after admission. Sixty STEMI patients after primary coronary angioplasty were selected, and used propensity score matching to compare patients treated with strong statin (n = 30), and those who did not (n = 30). Moreover, echocardiographic left ventricular (LV) parameters were determined, and plasma procollagen type III amino terminal peptide (PIIINP) was also measured before and 3 weeks after treatment.**

Results. **Following primary angioplasty, age, gender, risk factors, culprit coronary artery, peak serum creatine phosphokinase concentration, and recanalization time were similar in the two groups. However, the statin group showed significantly lower delayed total defect score and washout rate evaluated by ^{123}I-MIBG scintigraphy (22.4 ± 8.1 vs. 29.6 ± 10.5; $P < 0.01$, and 30.4 ± 8.9% vs. 40.1 ± 11.4%; $P < 0.005$, respectively) and higher delayed heart/mediastinum count ratio (2.17 ± 0.38 vs. 1.96 ± 0.30, $P < 0.05$) compared with the non-statin group. Moreover, the degree of change in LV parameters and PIIINP was more favorable in the statin group than in the non-statin group.**

Conclusions. **Administration of statin improves CSNA after reperfusion therapy in patients with first STEMI. (J Nucl Cardiol 2019)**

Key Words: Myocardial infarction • sympathetic nervous system • scintigraphy • statin

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The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations.

Reprint requests: Shu Kasama, MD, Institute for Clinical and Translational Science, Nara Medical University Hospital, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan; *s-kasama@bay.wind.ne.jp*
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Abbreviations	
CSNA	Cardiac sympathetic nerve activity
STEMI	ST-segment elevation myocardial infarction
MIBG	Metaiodobenzylguanidine
LV	Left ventricular
PIIINP	Procollagen type III amino terminal peptide
H/M	Heart/mediastinum count
WR	Washout rate
TDS	Total defect score
RDS	Regional defect score
RDSI	Regional defect score index

INTRODUCTION

Advances in percutaneous coronary interventions, such as the development of antithrombotic and stent therapies, have decreased mortality and morbidity in patients with acute myocardial infarction.[1,2] However, the development of heart failure following acute myocardial infarction, which is often accompanied by left ventricular (LV) remodeling, occurs in the chronic phase and often remains refractory to conventional drug therapy. Moreover, activation of cardiac sympathetic nerve activity (CSNA) is one of the pathophysiologic abnormalities associated with heart failure.[3]

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.[4-6] Statins effectively reduce the low-density lipoprotein cholesterol (LDL-C) level; in addition, they have other potentially favorable effects, which reduce cardiac events in patients with ischemic heart disease.[7,8] Furthermore, the efficacy of immediate statin administration in patients with ST-segment elevation myocardial infarction (STEMI) has been reported previously.[9] In that report, statin treatment improved cardiac systolic function and prevented LV remodeling following primary coronary angioplasty in patients with STEMI.

Myocardial imaging with ^{123}I-metaiodobenzylguanidine (MIBG), an analog of norepinephrine, is useful for detecting abnormalities in the myocardial adrenergic nervous system in patients with acute myocardial infarction.[10] The myocardial ischemic area and cardiac ^{123}I-MIBG defect size are correlated in patients undergoing reperfusion therapy for acute coronary syndromes.[11] This imaging modality has been reported to be useful for predicting the adverse cardiac events in patients with STEMI.[12] Based on cardiac ^{123}I-MIBG scintigraphy, many studies have suggested that cardioprotective treatment can improve CSNA in patients with various heart disease.[13-18] Moreover, previous studies reported that statin normalizes autonomic neural control in experimental heart failure,[19] and attenuates enhanced CSNA in animal models of myocardial infarction.[20] These favorable effects were associated with the increased myocardial uptake of norepinephrine mediated by this agent.[20,21] However, to our knowledge, no studies have examined the effects of statin treatment on CSNA evaluated by ^{123}I-MIBG scintigraphy in patients with STEMI.

Accordingly, we performed using our previously reported data[12] to evaluate the hypothesis that statin treatment improves CSNA in patients with a first STEMI undergoing primary coronary angioplasty.

MATERIALS AND METHODS

Patient Population

The consecutive patients with LDL-C < 120 mg/dL admitted to our institution for STEMI were considered the study population. This study was sub-analysis using our previous database.[12] The diagnosis of STEMI was made on the basis of chest pain > 30 minutes in duration, ST-segment elevation > 2 mm in two electrocardiographic leads, and more than threefold increase in serum creatine phosphokinase activity. In the acute phase, all patients were treated in standard fashion, including percutaneous coronary intervention. Patients were excluded from the study if they had primary hepatic failure, severe renal failure, or active cancer. Moreover, patients with severe heart failure requiring mechanical support (mechanical ventilation, intraaortic balloon pumping, left ventricular assist device, or cardiac resynchronization therapy) and those requiring heart transplantation were excluded.[12] Patients treated with tricyclic antidepressant drugs, serotonin reuptake inhibitors, or other psychotropic medications as known to interfere with cardiac ^{123}I-MIBG scintigraphic findings[22] were also excluded.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study Protocol

All patients underwent cardiac catheterization using the femoral and/or radial approach after an injection of 100 U/kg of heparin. The infarct-related artery was visualized using contrast injections. Patients with persistent occlusion of the infarct-related vessel underwent percutaneous coronary intervention by standard techniques. All patients received oral antiplatelet agents. If necessary, patients were also started, and

Table 1. Clinical characteristics and LV parameters of patients in both groups

	Statin (n = 30)	Non-statin (n = 30)	*P* value
Age (years)	69 ± 9	68 ± 12	0.882
Gender			0.779
Male	22 (73%)	20 (66%)	
Female	8 (27%)	10 (34%)	
Culprit coronary artery			
LAD	16 (53%)	15 (50%)	0.796
RCA	12 (40%)	11 (36%)	0.791
LCX	2 (7%)	4 (14%)	0.202
Current smoker	20 (66%)	18 (60%)	0.789
Diabetes mellitus	12 (40%)	10 (34%)	0.789
Hypertension	25 (83%)	22 (73%)	0.532
LDL-C > 120 mg/dL (at the time of entry)	0 (0%)	0 (0%)	1.000
Recanalization time (h)	3.7 ± 1.3	3.8 ± 1.2	0.758
Stent implantation	29 (96%)	28 (93%)	0.573
Peak CPK (IU/L)	3298 ± 1796	3342 ± 1982	0.929
In-hospital medications			
ACE-inhibitor or ARB	27 (90%)	28 (93%)	0.640
Beta-blocker	25 (83%)	26 (86%)	0.573
Calcium antagonist	8 (26%)	6 (20%)	0.761
Diuretics	7 (23%)	6 (20%)	0.754
Statin	30 (100%)	0 (0%)	-
Rosuvastatin	22 (74%)	0 (0%)	-
Atorvastatin	5 (16%)	0 (0%)	-
Pitavastatin	3 (10%)	0 (0%)	-

Data are presented as the mean value ± SD
LAD, left anterior descending coronary artery; *RCA*, right coronary artery; *LCX*, left circumflex coronary artery; *CPK*, creatine phosphokinase; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker

continued on an oral angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker, and/or a beta-adrenergic agent, as shown in Table 1. We measured the plasma concentration of procollagen type III amino terminal peptide (PIIINP) and performed echocardiography before primary coronary angioplasty.

A series of follow-up examinations (measurement of PIIINP concentrations and echocardiography) were repeated 3 weeks after angioplasty. We also performed ^{123}I-MIBG scintigraphy at the same time. The serum levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol, and LDL-C were also measured before and after 3 weeks of treatment.

In our database, statins were started after admission for many patients according to the guidelines (Guideline on the Management of Blood Cholesterol).[23] Therefore, the small number of patients did not receive statins for some reasons (i.e., muscle-related adverse events, liver dysfunction, or due to other statin intolerance). There were only 30 patients without statin treatments who met our inclusion criteria, so 30 patients were selected using propensity score matching from the statin-treated group. The statin agents included in this study were rosuvastatin (n = 22), atorvastatin (n = 5), and pitavastatin (n = 3).

Cardiac ^{123}I-MIBG Scintigraphy

The method used to conduct ^{123}I-MIBG imaging has been described previously.[15-17] Briefly, ^{123}I-MIBG was obtained from a commercial source (FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan). At 15 minutes and 4 hours after injection, anterior planar and SPECT images were obtained by the standard gamma camera (Millennium MPR, GE Medical Systems, Waukesha, Wisconsin).

The heart/mediastinum count (H/M) ratio was determined from the anterior planar delayed ^{123}I-MIBG image. The washout rate (WR) was calculated from early and delayed planar images. The delayed myocardial SPECT images of each patient were divided into the 17 segments recommended by the

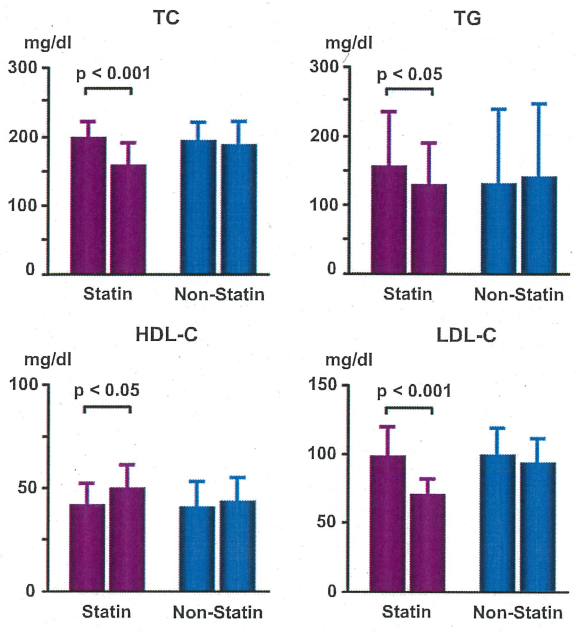

Figure 1. Changes in the serum levels of TC, TG, HDL-C, and LDL-C in the two groups from baseline to three weeks after treatment. Pink bars indicate the statin group, and the sky blue bars indicate the non-statin group. *TC*, total cholesterol; *TG*, triglyceride; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, lower low-density lipoprotein cholesterol.

American Heart Association. Tracer uptake in each segment was assessed semiquantitatively using a 5-point scoring system (0 = normal uptake; 1 = mildly reduced uptake; 2 = moderately reduced uptake; 3 = significantly reduced uptake; 4 = no uptake). Total defect score (TDS) was calculated as the sum of all defect scores.

The regional defect score (RDS) for each of the 17 segments was calculated to evaluate regional adrenergic dysfunction in our STEMI patients on SPECT images. Then the infarcted RDS index (RDSI) was calculated as the average RDS of the culprit segments. The non-infarcted RDSI was also calculated as the average RDS of the non-culprit segments.

Echocardiography

Echocardiography was performed using standard methods in a blinded manner, before and 3 weeks after angioplasty. The LV end-diastolic volume, end-systolic volume, and ejection fraction were calculated using the 2D-biplane method.[24]

Plasma PIIINP Concentrations

Blood samples were collected from an antecubital vein. The PIIINP plasma levels were measured by a specific immunoradiometric assay using a commercial kit (CIS Bio International, Nagoya, Japan), as previously reported.[25,26]

Statistical Analysis

The analyses were performed using SPSS version 25 (IBM Corp, Chicago, IL), or SAS version 9.4 (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.[27] 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, smoking, ^{123}I-MIBG scintigraphic and echocardiographic parameters, and the presence of diabetes and hypertension. Patients in the statin and non-statin groups were matched one to one to an accuracy of two digits, using the estimated propensity score for treatment with or without oral statin. In our database, 30 patients with STEMI were selected with the non-statin group, thus 30 matched patients were extracted from the statin group.

Categorical data were compared between the two groups using two-sided χ^2 tests, and differences between continuous variables were evaluated using the unpaired t test. Deviations from the group baseline were evaluated using a paired t test, and between the two groups using two-way ANOVA.

RESULTS

Clinical Characteristics

Neither significant differences were observed in the clinical characteristics nor cardiac medications were found between the two groups. Age, gender, culprit coronary artery, risk factors, recanalization time, and peak creatine phosphokinase concentrations in the acute phase were similar for both groups (Table 1). There were no differences in the in-hospital medications and clinical follow-up of the two study groups. The mean daily dose of enalapril, perindopril, and lisinopril in the statin and the non-statin groups were 8.0 and 8.2 mg, 3.1 and 3.2 mg, and 7.6 and 7.5 mg, respectively. The mean dose of candesartan and valsartan in the both groups were 7.8 and 7.5 mg, and 96 and 100 mg, respectively. The mean dose of carvedilol and bisoprolol in the both

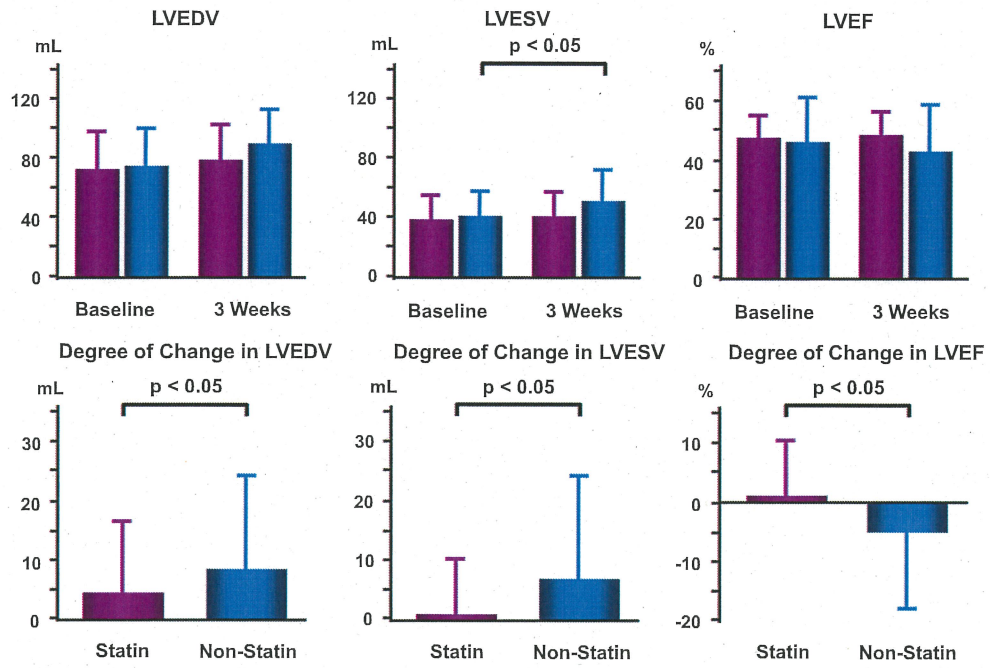

Figure 2. Changes in the LVEF, LVEDV, and LVESV in the two groups from baseline to three weeks after treatment (top). The degree of changes (value at 3 weeks minus baseline) in the LVEF, LVEDV, and LVESV (bottom). Pink bars indicate the statin group, and the sky blue bars indicate the non-statin group.

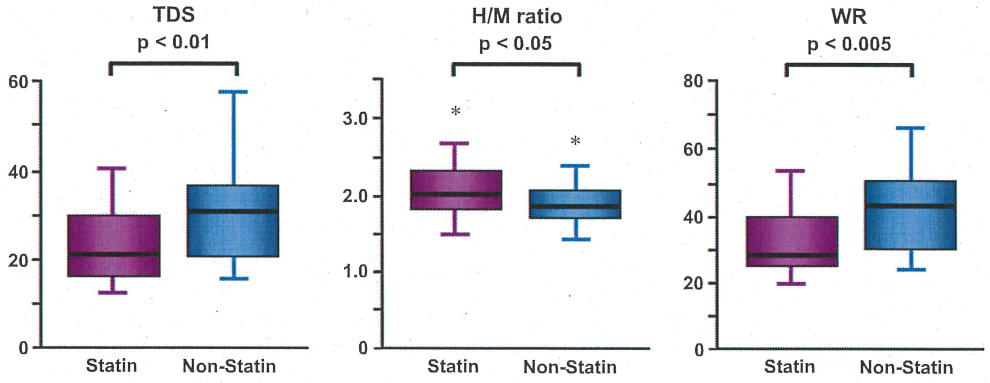

Figure 3. Comparison of cardiac ^{123}I-metaiodobenzylguanidine scintigraphic findings three weeks after treatment for TDS, H/M ratio, and WR in the two groups. Box plot presents median values as horizontal lines and mean values as plus signs within each box. The 25th and 75th quartiles are represented by the bottom and top of each box. An asterisk represents a possible outlier value. *TDS*, total defect score; *H/M*, heart/mediastinum count; *WR*, washout rate.

groups were 10.0 and 11.4 mg, and 3.7 and 3.8 mg, respectively. For our study protocol,[12] these agents were started as soon as possible after hospitalization, and continued during the study period. There were no differences in medication dose (including other drugs), and duration between the two groups (all, P = NS).

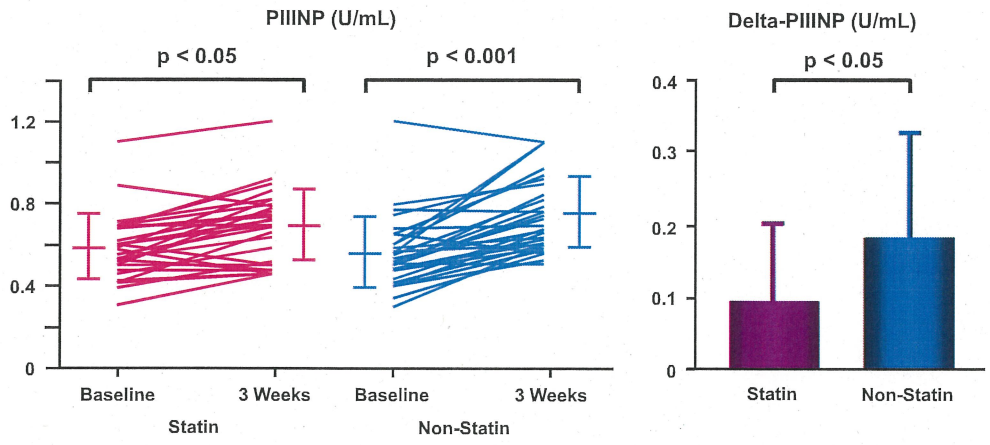

Figure 4. Changes in PIIINP concentrations from baseline to three weeks after treatment (left side) and the degree of change in PIIINP concentrations (right side). Pink bars indicate the statin group, and the sky blue bars indicate the non-statin group. *PIIINP*, procollagen type III aminoterminal peptide.

Table 2. MIBG scintigraphic parameters of patients in both groups

	Statin (n = 30)	Non-statin (n = 30)	*P* value
Global analysis			
TDS	22.4 ± 8.1	29.6 ± 10.5	< 0.01
H/M ratio	2.17 ± 0.38	1.96 ± 0.30	< 0.05
WR	30.4 ± 8.9	40.1 ± 11.4	< 0.005
Regional analysis			
Infarcted RDSI	2.8 ± 0.6	3.3 ± 0.7	< 0.01
Non-infarcted RDSI	0.7 ± 0.3	1.2 ± 0.5	< 0.005

Data are presented as the mean value ± SD
TDS, total defect score; *H/M*, heart/mediastinum count; *WR*, washout rate; *RDSI*, regional defect score index

Comparison of Lipid Levels at Baseline and 3 Weeks After Treatment

As shown in Figure 1, the serum concentrations of total cholesterol, triglyceride, and LDL-C were significantly decreased in the statin group after 3 weeks of treatment, while high-density lipoprotein cholesterol concentrations were significantly increased. In contrast, these parameters did not change significantly in the non-statin group.

Comparison of LV Parameters at Baseline and 3 Weeks After Treatment

The LV end-diastolic volumes, end-systolic volumes, and ejection fractions are shown in Figure 2. In the statin group, these parameters did not change significantly after 3 weeks of treatment. In contrast, the LV end-systolic volume was significantly increased in the non-statin group. Moreover, the degree of change in LV ejection fraction, end-diastolic volume, and end-systolic volume in the statin group was more favorable than in the non-statin group.

Comparison of Cardiac ^{123}I-MIBG Scintigraphic Findings 3 weeks After Treatment

The TDS, H/M ratio, and WR are shown in Table 2 and Figure 3. The TDS in the statin group was significantly lower than in the non-statin group ($P < 0.01$).

The H/M ratio in the statin group was significantly higher than in the non-statin group ($P < 0.05$). The WR in the statin group was significantly lower than in the non-statin group ($P < 0.005$).

Table 2 provides a summary of infarcted RDSI and non-infarcted RDSI. The infarcted RDSI in the statin group was significantly lower than in the non-statin group ($P < 0.01$). Finally, non-infarcted RDSI was also significantly lower than in the non-statin group ($P < 0.005$).

Comparison of PIIINP Concentrations at Baseline and 3 Weeks After Treatment

PIIINP concentrations are shown in Figure 4. In both groups, the plasma PIIINP concentrations were significantly increased after 3 weeks of treatment ($P < 0.05$ in the statin group and $P < 0.001$ in the non-statin group). However, the change in PIIINP in the statin group was significantly lower than that observed in the non-statin group ($P < 0.05$) (Fig. 4).

DISCUSSION

The findings of this study demonstrate for the first time that the statin treatment can improve CSNA and prevent LV remodeling in patients with a first STEMI, as compared to standard conventional therapy alone. This agent can also suppress cardiac collagen synthesis during the acute to subacute phase of STEMI, following primary coronary angioplasty.

Inflammatory cytokines play an important role in the development and progression of human heart failure. They have been implicated in the development of LV remodeling, endothelial dysfunction, and increased cardiac myocyte apoptosis.[28] As statins have well-characterized anti-inflammatory effects and downregulate inflammatory cytokines in the failing heart,[29] they may attenuate LV global remodeling. In general, changes in LV volume have been shown to be associated with prognosis in patients with acute myocardial infarction.[30] In this study, LV volumes were significantly increased in the non-statin group after three weeks; however, these parameters did not change in the statin group. Therefore, adding statin to standard therapy may attenuate LV volume changes after reperfusion therapy in patients with STEMI.

^{123}I-MIBG, an analog of the adrenergic neuron-blocking agent guanethidine is thought to utilize the same mechanism of myocardial uptake and release as norepinephrine.[31] Cardiac ^{123}I-MIBG imaging may provide a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with acute myocardial infarction.[10-12] Moreover, the release of norepinephrine was reported to be enhanced, and the uptake of norepinephrine is also reduced, in the ischemic heart.[32] Kang et al[21] demonstrated that the release and uptake of norepinephrine are modulated by activation of adenosine triphosphate-sensitive potassium (K-ATP) channels in experimental rat models. As statin is reported to activate K-ATP channels,[20] increase myocardial perfusion,[32] and improve oxygenation in the ischemic myocardium,[33] this agent may comprehensively attenuate enhanced CSNA. Therefore, we hypothesize that the statin treatment can improve CSNA in patients with STEMI. In this study, the TDS, H/M ratio, and WR determined by cardiac ^{123}I-MIBG scintigraphy were improved in the statin group, as compared to the standard conventional therapy group.

On the other hand, we previously reported that ^{123}I-MIBG scintigraphic parameters three weeks after the onset of STEMI provide useful predictors of cardiac events in patients with STEMI.[12] In that report, we concluded that the WR was a powerful predictor of both cardiac death and major adverse cardiac events in 213 patients with STEMI. As a result, we had made more efforts towards the pharmacological improvement of CSNA. This study found that adding statin to standard therapy had beneficial effects on ^{123}I-MIBG scintigraphic findings, as compared with conventional therapy alone. Therefore, our findings demonstrate for the first time that statin treatment had beneficial effects on the CSNA in patients with STEMI, indicating that this may improve patient outcomes, as shown previously.[4-6]

It is known that regional sympathetic denervation is associated with contractile dysfunction and myocardial fibrosis in patients with heart failure.[34] Moreover, very interestingly, Kramer et al[35] reported that increased sympathetic denervation in adjacent non-infarcted regions evaluated by ^{123}I-MIBG scintigraphy leads to LV remodeling after acute myocardial infarction. In this study, both infarcted and non-infarcted RDSI in the stain group were significantly lower than those in the non-statin group. We suggest that adding statin to standard therapy not only improves CSNA, but also attenuates myocardial fibrosis and prevents LV remodeling, as compared with standard conventional therapy following reperfusion in patients with STEMI. However, further study will be required to confirm this hypothesis.

Plasma PIIINP concentrations may constitute a biochemical marker for myocardial fibrosis or LV remodeling in patients with failing heart.[36,37] Klappacher et al[36] reported the significant positive correlation between plasma PIIINP and the amount of myocardial collagen type III on cardiac biopsy specimens of heart failure patients. Moreover, Host et al[37] showed that the plasma PIIINP was higher in those patients with a poor prognosis after myocardial

infarction. We have previously focused on the plasma PIIINP as the biochemical marker of myocardial fibrosis and/or left ventricular remodeling. Therefore, we reported the association between plasma PIIINP concentrations and ^{123}I-MIBG scintigraphic parameters after medical treatments in STEMI patients.[25,26] In the present study, the plasma PIIINP concentrations in the acute phase were significantly increased after 3 weeks in both groups. However, the degree of change in PIIINP was significantly lower in the statin group than in the non-statin group.

STUDY LIMITATIONS

The small number of patients with STEMI included in this study was a limitation. Moreover, we did not perform cardiac sympathetic nervous PET imaging. The evaluations of CSNA by PET imaging have been advocated to provide a more detailed, regional analysis of the myocardium, compared with cardiac ^{123}I-MIBG scintigraphy.[34,38] However, the cardiac sympathetic nervous PET imaging has yet to achieve broad clinical acceptance, because of demand for costly on-site cyclotrons, which are required for production of conventional ^{11}C-labeled (radiological half-life, 20 minutes) PET tracers. Therefore, future studies should examine the effects of statin on CSNA evaluated using PET imaging in a larger group of patients.

NEW KNOWLEDGE GAINED

While it is known that the cardioprotective treatments can improve CSNA evaluated by ^{123}I-MIBG scintigraphy in patients with STEMI, we have shown that statins have similar effects. Therefore, statins may be effective for reducing the incidence of cardiac events for these patients.

CONCLUSIONS

The TDS, H/M ratio, and WR determined by cardiac ^{123}I-MIBG scintigraphy were improved by use of statin, as compared with the standard conventional therapy. Three weeks after treatment, LV parameters in the statin group are more favorable than those in the conventional therapy group. These findings indicate that administration of statin can improve CSNA and prevent LV remodeling in patients with a first STEMI.

Disclosure

The authors have declared that they have no financial conflicts of interest.

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