Effect of Rosuvastatin on Cardiac Remodeling, Function, and Progression to Heart Failure in Hypertensive Heart With Established Left Ventricular Hypertrophy

Sung-A Chang, Yong-Jin Kim, Hye-Won Lee, Dae-Hee Kim, Hyung-Kwan Kim, Hyuk-Jae Chang, Dae-Won Sohn, Byung-Hee Oh, Young-Bae Park

Abstract—Hypertensive patients with left ventricular hypertrophy (LVH) are the most common high-risk group to develop heart failure with preserved ejection fraction. Recent reports have noted the favorable effect of statins on LVH. We evaluated the effect of rosuvastatin on cardiac remodeling, function, and progression to heart failure in a hypertensive rat model with established LVH. Dahl salt-sensitive rats were fed a high-salt diet until 13 weeks of age. After LVH was confirmed by echocardiography, rats were randomly assigned to control and statin treatment (n=18 each group). The statin-treated group was treated with rosuvastatin until 21 weeks of ages. Serial echocardiography, blood pressure monitoring, and miniaturized conductance catheter hemodynamic monitoring were performed at 21 weeks. Echocardiographic parameters were not significantly different between the groups. On hemodynamic monitoring, systolic performance parameters were similar between the groups, whereas end diastolic pressure-volume relationships were lower in the statin-treated group (0.014±0.008 versus 0.008±0.004 mm Hg/μL, P<0.05), suggesting improvement in myocardial stiffness. Pathological analysis showed attenuation of perivascular and interstitial fibrosis in the statin-treated group (P<0.02). Rosuvastatin therapy did not alleviate LVH in hypertensive rats with established LVH, but it attenuated myocardial fibrosis and LV stiffness. It seems that rosuvastatin has limited therapeutic value when used to prevent progression from LVH to heart failure in hypertensive hearts. (Hypertension. 2009;54:591-597.)

Key Words: heart failure ■ ventricular hypertrophy ■ hypertension ■ statin

Heart failure (HF) is one of the most common causes of cardiovascular morbidity and mortality, and its prevalence is rapidly increasing as the mean age of the population advances.1 Half of the patients with HF have been shown to have preserved left ventricular (LV) systolic function, (ie, HF with preserved LV ejection fraction [HFPEF]).2 The mortality associated with HFPEF is estimated to be 5% to 8% annually, which is similar to that of systolic HF.3,4 Hypertensive patients with LV hypertrophy (LVH) are at a high risk to develop HFPEF.5 Chronic pressure-overload initially induces compensated LVH but eventually causes tissue fibrosis and myocyte damage that lead to HF. Blood pressure reduction is the primary treatment for hypertensive cardiomyopathy, but LVH occasionally persists and patients are still at risk for HF.6

The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, commonly referred to as statins, are well-known potent lipid lowering agents. In addition to their primary effects, the statins have been shown to have pleiotropic effects on the cardiovascular system,7 including antiinflammatory, antioxidative, and endothelial protective effects and thus have been tested as a therapeutic agent in HF.2,8 Although recent large clinical trials have failed to demonstrate the benefits of statins in HF,9 these results cannot be directly applied in HFPEF because the majority of the study population in these studies had systolic HF. In addition, recent clinical studies and experimental studies have suggested the beneficial effects of statin therapy in HFPEF.9–11

Dahl-Iwai salt-sensitive rats are a well-established model of hypertensive cardiomyopathy. As previously reported,12,13 these rats develop hypertension when fed an 8% NaCl diet from 7 weeks of age and have compensated LVH at 13 weeks of age. This is a well defined hypertensive model which shows myocardial fibrosis, myocardial stiffness, and overt heart failure at 20 weeks of age.13 We performed animal studies using Dahl-Iwai salt-sensitive rats to evaluate the effect of rosuvastatin on cardiac remodeling, function, and progression to HF in hypertensive hearts with established LVH.

Methods

Animal Model
Dahl-Iwai salt-sensitive rats (DIS/Eis, Eisai, Tokyo, Japan) were fed a low-salt diet (0.3% NaCl) from weaning until 7 weeks of age.
Thereafter, 6 animals were fed a low-salt diet until 13 weeks of age (defined as the low-salt group) to confirm the model of hypertensive animals developing LVH. The high-salt group (n=36) were fed laboratory chow containing 8% NaCl (high salt diet) from 7 weeks to 13 weeks of age.

At 7 and 13 weeks, echocardiography and noninvasive blood pressure monitoring were performed to confirm the development of hypertension and LVH in the high-salt group. After confirming the development of LVH in the high-salt group, the rats were divided into 2 subgroups (control and statin-treated group) in a random manner.

Rosuvastatin (AstraZeneca, 20 mg/kg/d) or vehicle were administered orally by gavage from 13 to 21 weeks of age. The statin dose was based on a previous study showing a beneficial pleiotropic vascular effect in a hypertensive model.

All of the rats were housed in the Laboratory Animal Facility of the Clinical Research Institute of Seoul National University. The study protocol was approved by the Institutional Animal Care and Use Committee of Seoul National University.

Noninvasive Blood Pressure Monitoring
Systolic and diastolic blood pressures were measured conscious rats by the tail-cuff method (Biopac System Inc) at 13, 17, and 21 weeks, 1 day after echocardiographic examination to minimize the stress imposed on the animals.

Echocardiographic Measurements
Echocardiography was performed at 7, 13, 17, and 21 weeks of age. The rats were lightly sedated with intraperitoneal zoletapam (Zoetil, 25 mg/kg). Images were acquired with a 12 MHz transducer connected to a Vivid-i echocardiography machine (GE Medical). M-mode and 2-dimensional echocardiography images were acquired at the papillary muscle level with a frame rate of 80 to 120/s. LV end-diastolic septal and posterior wall thickness (SWT and PWT), LV end-diastolic dimension (LVEDD), and LV end systolic dimension (LVESD) were measured. The LV ejection fraction (LVEF) was calculated according to the following formula: 

\[
\text{LVEF} = \frac{\text{LVESD}}{\text{LVEDD}} \times 100\%
\]

The LV mass was estimated by a formula previously validated in small animals:

\[
\text{LV mass} = \left(\frac{\text{SWT} + \text{LV PW} + \text{LVEDD}}{\text{LVEDD}}\right)^3 - \left(\frac{\text{LVEDD}}{\text{LVEDD}}\right)^3 \times 0.8 + 0.14 \text{ g}
\]

Doppler examination was performed from the apical 4-chamber view by using a pulsed-wave Doppler with a sample volume of 2 mm to obtain deceleration time (DT), early and late transmitral velocity (E and A wave), and their ratio (E/A ratio). The septal mitral annulus velocity (E') was assessed by tissue Doppler imaging with a sample volume of 1.5 mm. All parameters were evaluated on an average of 3 consecutive beats. A single echocardiographer who was blinded to the treatment information performed all data acquisition.

Hemodynamic Measurements
The rats were anesthetized with intraperitoneal zoletapam (Zoetil, 25 mg/Kg) and ventilated. An anterior thoracotomy was performed, and a small apical stab was made to expose the LV apex. Hemodynamic measurement was performed by the microtip P-V catheter (SPR-838, Millar Instruments), which was inserted retrograde into the LV cavity as previously described (supplemental detailed methodology, available online at http://hyper.ahajournals.org). Polyanethylene catheters (PE-50) were inserted for measurement of the mean arterial pressure. The right internal jugular vein was used as a central venous line for fluid administration. The inferior vena cava (IVC) and portal vein were exposed, and then a snare suture was placed to modulate the rapid IVC obstruction. All loops were acquired after 20 minutes of stabilization with the ventilator turned off for 5 to 10 seconds. The sampling rate was 1000/s using the ARIA P-V conductance system (Millar Instruments) coupled to a PowerLab/4SP A/D converter (AD Instruments) and a personal computer. After the data were recorded under steady state and preload reduction by IVC ligation, parallel conductance (Vp) was obtained by injecting 500 μL of 15% hypertonic saline into the central venous line.

Volume calibration was performed using aortic flow calibration with a perivascular flow probe and flowmetry (T-106, Transonic Inc), and correction with Vp was performed as previously described. Analysis of the loops was performed using a commercially available cardiac P-V analysis program, PVAN3.5 (Millar Instruments). Heart rate, maximal LV systolic pressure, LV end-diastolic pressure (EDP), mean arterial pressure, maximal slope of systolic pressure increment (+dP/dt) and diastolic pressure decrement (−dP/dt), time constant of LV pressure decay (τ), EF, stroke volume, end-diastolic volume (EDV), cardiac index (CI), and stroke work (SW) were all calculated.

LV P-V relations were measured via transient occlusion of the IVC with a silk snare suture. Ten to 20 successive cardiac cycles were obtained over 5 seconds, from which the end-systolic pressure volume relation (ESPVVR) slope, SW-EDV relation (preload recruitable stroke work [PRSW]), slope of the maximum first derivative of ventricular pressure with respect to time (dP/dtmax)-EDV relation, and end-diastolic pressure volume relation (EDPVR) slopes were derived.

Histological Analysis
After hemodynamic measurements were performed, the rats were euthanized and the hearts and lungs were harvested. The ventricles were rinsed with isotonic saline then dissected and weighed, as were the lungs. The weights of the total heart and lung were normalized to the body weight and used as an index of ventricular hypertrophy and pulmonary congestion, respectively.

The LV was then fixed with 4% paraformaldehyde, dehydrated with sucrose, and embedded in paraffin, as previously described. The tissue was sectioned into 4-μm slices, and stained with Masson trichrome for evaluation of fibrosis and with picrosirius red for evaluation of collagen deposition. Quantitative measurement of the area of perivascular fibrosis was calculated as the ratio of the area of fibrosis surrounding the vessel wall to the total vessel area using an imaging analysis program (Image J ver. 1.38, NIH). At least 10 arterial cross sections were examined per heart. The area of interstitial fibrosis and collagen deposition was identified after excluding the vessel area from the region of interest, as the ratio of interstitial fibrosis or collagen deposition to the total tissue area. At least 3 sections were examined per heart.

Arterial blood sample was collected from the abdominal aorta immediately after hemodynamic measurement. Serum was isolated and assayed for total cholesterol, high-density lipoprotein cholesterol, and triglycerides using enzymatic methods. All statistical analyses were performed using SPSS 13.0 (SPSS Inc), with probability values <0.05 considered statistically significant.

Results
At 13 weeks, the rats in the high-salt group developed hypertension and LVH (supplemental Table S1). LV EF did not differ with diet, but E/A was decreased and E/e', which is a noninvasive method for estimating LV filling pressure, was higher with borderline significance.

After confirmation of the model of LVH at 13 weeks of age, rats on the high-salt diet were randomly allocated to control and statin treatment. Table 1 shows that there were no differences in the baseline characteristics between the 2 treatment groups.

High blood pressure was maintained during the study period, and the statin did not influence the blood pressure per serial NIBP monitoring (Figure 1A). Serial echocardiography showed no differences in LV wall thickness between the control and statin-treated groups (Figure 1B), and LVEF was
preserved in both groups (Figure 1C). The deceleration time (DT) was prolonged in both groups (Figure 1D).

At 21 weeks of age, both the control and statin-treated groups developed HF with elevated LV EDP and increased wet lung weights (supplemental Table S2). Table 2 shows that at the age of 21 weeks, the body weight, heart weight/body weight, and wet lung weight/body weight were not different between the groups. Five of 18 rats in each groups died during the study period. Therefore the survival rate in the control and statin-treated groups did not show a significant difference (n=13 in control and n=13 in statin-treated group).

Table 3 summarizes the main hemodynamic parameters in the control and statin-treated groups. The heart rate and mean arterial pressure did not differ in the 2 groups. On steady state analysis, LV EDV, LV EDP, CI, SWI, \( dP/dt \), \( dP/dt \), and \( EDPVR \) slope, PRSW, and \( dP/dt_{max} \)-EDV relationship were not different between the 2 groups (Table 3). However, the \( EDPVR \) slope was decreased in the statin-treated group (0.014 ± 0.008 versus 0.008 ± 0.004 mm Hg/µL, \( P=0.01 \)), indicating decreased diastolic LV stiffness.

Table 1. General and Echocardiographic Characteristics at 13 Weeks of Age

<table>
<thead>
<tr>
<th>Variables</th>
<th>High-Salt Diet</th>
<th>Selected for Control Group (n=18)</th>
<th>Selected for Statin Treatment (n=18)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP, mm Hg</td>
<td>143.6±23.4</td>
<td>144.6±21.9</td>
<td>0.90</td>
<td></td>
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<tr>
<td>Systolic BP, mm Hg</td>
<td>182.2±24.1</td>
<td>181.4±13.0</td>
<td>0.90</td>
<td></td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>124.8±25.9</td>
<td>126.3±28.9</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>223.3±24.5</td>
<td>230.7±40.9</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Body weight, g</td>
<td>324.7±19.3</td>
<td>323.9±21.0</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>75.1±74.3</td>
<td>74.3±7.8</td>
<td>0.76</td>
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<tr>
<td>SWT, mm</td>
<td>2.21±0.25</td>
<td>2.09±0.21</td>
<td>0.12</td>
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</tr>
<tr>
<td>PWT, mm</td>
<td>2.19±0.29</td>
<td>2.01±0.32</td>
<td>0.10</td>
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<tr>
<td>EDD, mm</td>
<td>7.14±0.65</td>
<td>7.36±0.74</td>
<td>0.34</td>
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<tr>
<td>ESD, mm</td>
<td>4.34±0.73</td>
<td>4.52±0.85</td>
<td>0.50</td>
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</tr>
<tr>
<td>E/A</td>
<td>1.46±0.27</td>
<td>1.56±0.52</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>E/E'</td>
<td>24.74±8.51</td>
<td>22.90±9.78</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>LV mass, g*</td>
<td>1.12±0.15</td>
<td>1.06±0.16</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

Data are means±SD. BP indicates blood pressure measured in conscious rats by noninvasive tail-cuff method; HR, heart rate; EF, ejection fraction; SWT, end-diastolic wall thickness of interventricular septum; PWT, end diastolic wall thickness of posterior wall; EDD, end diastolic dimension; ESD, end systolic dimension; E/A, mitral inflow E-A ratio; E/E', mitral inflow E-septal tissue Doppler velocity E' ratio.

*LV mass was estimated in vivo by echocardiography.

Table 2. Results of Pathology

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (n=13)</th>
<th>Statin-Treated Group (n=13)</th>
<th>( P ) Value</th>
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<tr>
<td>BW, g</td>
<td>375.7±28.5</td>
<td>382.9±35.5</td>
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<tr>
<td>Heart, g</td>
<td>1.46±0.09</td>
<td>1.46±1.26</td>
<td>1.00</td>
</tr>
<tr>
<td>Lung, g</td>
<td>1.84±0.19</td>
<td>1.79±0.26</td>
<td>0.57</td>
</tr>
<tr>
<td>Heart/BW, mg/g</td>
<td>3.91±0.41</td>
<td>3.83±0.51</td>
<td>0.66</td>
</tr>
<tr>
<td>Lung/BW, mg/g</td>
<td>4.93±0.66</td>
<td>4.68±0.70</td>
<td>0.36</td>
</tr>
<tr>
<td>Perivascular fibrosis, %</td>
<td>54.9±6.8</td>
<td>48.7±6.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Interstitial fibrosis, %</td>
<td>5.88±0.32</td>
<td>5.56±0.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Interstitial collagen, %</td>
<td>4.36±0.66</td>
<td>3.36±0.87</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are means±SD. BW indicates body wt.

Figure 1. Serial change in blood pressure and cardiac remodeling using echocardiographic measurement. A, BP, blood pressure. B, LV PWT, left ventricular posterior wall thickness. C, LV EF, LV ejection fraction. D, DT, deceleration time.
Pathological examination (Figure 3) showed that the extent of perivascular fibrosis was significantly smaller in the statin-treated group compared to the control group (P = 0.02; Table 2, Figure 3A, 3C, 3D, and 3F). Quantitative measurement of interstitial fibrosis showed differences between the statin-treated and control groups (Table 2, Figure 3B and 3E). Interstitial collagen was also less prominent in the statin-treated group (P = 0.01; Table 2, Figure 4). There was no difference between control and statin-treated group with regard to lipid levels (supplemental Table S3).

**Discussion**

The purpose of this study was to evaluate the effect of chronic administration of rosuvastatin on cardiac remodeling, function, and regression to HF in Dahl salt-sensitive rats with hypertension and LVH. Long-term administration of rosuvastatin in these rats did not attenuate LVH and did not improve LV filling pressure or contractility. Animal survival and lung congestion were the same regardless of rosuvastatin administration. Rosuvastatin therapy only attenuated myocardial fibrosis and improved LV stiffness.

The effect of statins on LVH regression, vascular function, and fibrosis has been reported in previous animal studies. However, there was disagreement among previous studies, possibly because of differences in animal models, statins, and experimental protocols. Frohlich et al noted no LVH regression with rosuvastatin treatment in spontaneous hypertensive rats or L-NAME-induced hypertensive rats. Animals showed improved peripheral vascular resistance, but there was no change in collagen content. In contrast, DOCA salt-induced hypertensive rats treated with rosuvastatin showed no change of vascular dysfunction but had attenuated cardiovascular fibrosis. In our study, peripheral resistance was not significantly different between the statin-treated and control groups, but the degrees of fibrosis and collagen deposition were significantly decreased. The differential effect of rosuvastatin on peripheral vascular resistance can be attributed to the different mechanisms of hypertension in experimental models. DOCA salt-induced hypertensive rats and Dahl salt-sensitive rats develop hypertension in a salt-dependent manner. Retention of salt and water is common in these models. On the other hand, SHR and L-NAME–induced hypertensive models involve naturally occurring or experimentally induced endothelial dysfunction, where the effect of statins on peripheral resistance may be more evident.

Perivascular and interstitial fibrosis were reduced in previous studies of Dahl salt-sensitive rats and DOCA salt-induced hypertensive rats. Survival rates were increased, LVH was attenuated, and cardiac systolic and diastolic function improved. However, results concerning the effect of statins on LVH regression and cardiac function have not been consistent. In our study, rosuvastatin did not cause attenuation of LVH. Although perivascular fibrosis was suppressed to a degree similar to earlier reports, the reduction in myocyte hypertrophy was not sufficient. In previous studies reporting the attenuation of LVH by statin therapy, the statin treatment was started during an earlier phase of LVH. In our study, the hypertensive stimulus persisted throughout the experiments, and the statin was administered after the establishment of LVH. Therefore, statin monotherapy might be less effective in established LVH in the absence of blood pressure control. Statin treatment initiated before the development of LVH might be more effective. Moreover, considering the inconsistent results from previous studies, the effect of statins on LVH regression might not be a general “statin” effect but rather a drug specific effect, which suggests that different statins may have different therapeutic indications.

The characteristic pathology of the LV structural changes in hypertensive patients includes cardiomyocyte hypertrophy and death, as well as tissue fibrosis. High blood pressure stimulates both fibroblasts and cardiomyocytes to express hormones and cytokines such as angiotensin II, TGF-β1, endothelin-1, and TNF-α. This is one of the important causes of myocardial stiffening, which is predominantly manifested during diastole, with consequent disturbances in calcium handling in the cardiomyocytes leading to cardiac dysfunction. Perivascular and interstitial fibrosis were found to be decreased in the statin-treated group in this study, although the absolute decrease was small. Some studies have reported that statin treatment does not alter blood pressure in Dahl salt-sensitive rats or DOCA salt-induced hypertensive
The same studies have shown decreased perivascular fibrosis in statin-treated rats. This strongly suggests that statins decrease the perivascular fibrosis in a blood pressure–independent manner; thus, statins have been suggested to modify the molecular process of fibrosis.

Proof of the underlying mechanism is beyond the scope of the present study, but previous studies focusing on the molecular etiology have suggested several possible mechanisms. Ruperez et al reported that statins decreased angiotensin II–induced fibrosis in in vitro experiments through suppression of RhoA/ROCK and MAPK pathways.27 Yagi et al reported that pitavastatin decreased perivascular fibrosis by eNOS-independent protective actions against angiotensin II–induced cardiovascular remodeling.28 Xu et al showed that the antifibrotic effects of pravastatin were closely associated with the downregulation of TGF-β, MMP2 and -3, and TNF-α.29 Suppression of the endothelin system by pitavastatin was also suggested as a possible mechanism.20

In the present study, Dahl salt-sensitive rats were used as a hypertensive cardiomyopathy model. These animals eventually progress to HF at the age of 21 weeks. HF presents as wet lungs and increased LVEDP. From this perspective, rosuvastin...
tatin treatment did not improve the HF in the hypertensive rats in this study when treatment was initiated after LVH development.

LV function in HFPEF continues to be debated. LV systolic performance may be preserved in HFPEF\textsuperscript{30} or depressed. Furthermore, HF can develop under preserved systolic and diastolic properties because of retained salt and water.\textsuperscript{13} These discrepancies are likely attributable to inherent limitations in the different methods used to measure LV function.\textsuperscript{30–33} Therefore, understanding of the parameters of LV function is crucial before the studies are interpreted. For example, LVEF, which can be easily acquired by 2D echocardiography, is a load-dependent parameter and is possibly misleading in cases with different loading conditions. Assessment of cardiac performance using conductance catheter system is invasive, but it is the most comprehensive methodology yet available that can derive the independent parameters from loading conditions by simultaneously quantifying load and the interaction of the heart and vasculature.\textsuperscript{17} In the present experiments, the effect of statin therapy on LV function in HFPEF was determined using a miniaturized conductance catheter system. The load independent parameters were not significantly different between the statin-treated and control groups, which suggests that statins do not change the LV contractile function of HFPEF in hypertensive rats.

Evaluation of diastolic properties was also performed. LVEDP and negative dP/dt showed no difference, but the EDPVR, which indicates diastolic stiffness, was lower in statin-treated rats. LVEDP and negative dP/dt are load-dependent parameters, but diastolic stiffness is independent of load. Therefore it has been suggested as a target for treating HFPEF.\textsuperscript{34} Passive stiffness is a passive viscoelastic property that returns the myocardium to its resting state. Increases in passive stiffness can be caused by abnormalities in the cardiomyocytes, extracellular matrix, or both.\textsuperscript{3} Perivascular fibrosis was decreased in the rosuvastatin-treated group, and this finding was probably associated with the decreased diastolic stiffness in the statin-treated group.

This limited efficacy of rosuvastatin in the treatment of HF after development of LVH is disappointing, but improvement of the myocardial stiffness in patients with hypertensive cardiomyopathy still endows it with therapeutic potency in clinical practice. Because myocardial stiffness plays an important role in exercise tolerance,\textsuperscript{35} it is impetuous to conclude that statin therapy is of little use in HFPEF in hypertensive cardiomyopathy. Even though rosuvastatin failed to improve the mortality of systolic HF patients\textsuperscript{4} and as well as in HFPEF of our animal models, the therapeutic effect of rosuvastatin on exercise capacity or quality of life in HFPEF needs further investigation.

There were some limitations to our study. First, the animal model in this study had persistently high blood pressure until 21 weeks of age. Therefore, the effect of hypertension on other end organs could have caused additional damage, such as renal dysfunction, and could possibly have resulted in a volume overload state that could have reduced the favorable effects of statin treatment. In this context, it is possible that statins are more effective with a low-salt diet. Second, we did not investigate the molecular biology of suppressed myocardial fibrosis with statin treatment. This should be addressed in future studies.

Perspectives

In summary, the therapeutic effect of rosuvastatin on the progression of established LVH to HF in hypertensive hearts has limited value. Rosuvastatin did not attenuate hypertension-induced LVH, though it improved the perivascular fibrosis. It showed no therapeutic efficacy to improve HF and survival. LV systolic function was not changed by the administration of rosuvastatin, but diastolic stiffness was...
decreased in the statin-treated group. Change of the myocardial stiffness in hypertensive cardiomyopathy might be associated with exercise tolerance or hospital revisits, which are closely associated with quality of life in the clinical setting. The clinical value of attenuated myocardial stiffness by rosuvastatin requires further investigation.

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**Disclosures**

None.

**References**


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Sung-A Chang, MD, PhD; Yong-Jin Kim, MD, PhD; Hye-Won Lee; Dae-Hee Kim, MD, PhD; Hyung-Kwan Kim, MD, PhD; Hyuk-Jae Chang, MD, PhD; Dae-Won Sohn, MD, PhD; Byung-Hee Oh, MD, PhD ;Young-Bae Park, MD, PhD
Cardiovascular Center, Seoul National University Hospital,
Department of Internal Medicine, Seoul National University College of Medicine,
Seoul, Korea

Short Title: Effect of Rosuvastatin on Hypertensive Heart

Address for correspondence:
Yong-Jin Kim, MD, PhD
Associate Professor
Department of Internal Medicine, Cardiovascular Center
Seoul National University Hospital
28 Yongon-dong, Chongno-gu, Seoul, 110-744, Korea
Tel: (82)(2) 2072-1963 , Fax: (82)(2) 2072-2577
E-mail:kimdamas@snu.ac.kr
Detailed Methodology

Surgical Procedure for Hemodynamic Monitoring

The rats were anesthetized with intraperitoneal zolazepam (Zoletil, 25mg/Kg) and placed in the recumbent position on a heat pad with a rectal probe connected to a thermoregulator. The animals were intubated with a blunt 16-gauge needle using the tracheotomy method and ventilated with a custom-designed constant-pressure ventilator at 75 breaths/min using room air. An anterior thoracotomy was performed and a small apical stab was made to expose the LV apex. Electrocautery was used to minimize bleeding during the surgical procedure.

After the apex of the LV was stabbed with a 27-gauge needle, the microtip P-V catheter (SPR-838, Millar Instruments; Houston, TX, USA) was inserted retrograde into the LV cavity along the cardiac longitudinal axis until stable P-V loops were obtained. Polyethylene catheters (PE-50) were inserted into the right femoral artery for measurement of the mean arterial pressure. The right internal jugular vein was used as a central venous line for fluid administration. The abdominal wall was opened, and the inferior vena cava (IVC) and portal vein were exposed. A snare suture was placed to modulate the rapid IVC obstruction. All loops were acquired after 20 minutes of stabilization with the ventilator turned off for 5-10 seconds. The sampling rate was 1,000/s using the ARIA P-V conductance system (Millar Instruments) coupled to a PowerLab/4SP A/D converter (AD Instruments; Mountain View, CA, USA) and a personal computer. After the data were recorded under steady state and preload reduction by IVC ligation, parallel conductance ($V_p$) was obtained by injecting 500μl of 15% hypertonic saline into the central venous line.
Table S1. Echocardiographic and General Information to confirm the LVH model (13 weeks of age)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low salt diet (n=6)</th>
<th>High salt diet (n=36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP, mmHg</td>
<td>103.6 ±29.6</td>
<td>144.1 ±22.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>136.9 ±27.0</td>
<td>181.8 ±18.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>87.1 ±31.1</td>
<td>125.6 ±27.1</td>
<td>0.001</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>228.7 ±16.0</td>
<td>227.1 ±33.6</td>
<td>0.552</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>339.7 ±22.1</td>
<td>324.3 ±19.9</td>
<td>0.076</td>
</tr>
<tr>
<td>EF, %</td>
<td>73.5 ±5.08</td>
<td>74.7 ±7.2</td>
<td>0.733</td>
</tr>
<tr>
<td>SWT, mm</td>
<td>1.78 ±0.15</td>
<td>2.15 ±0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>1.78 ±0.15</td>
<td>2.15 ±0.23</td>
<td>0.002</td>
</tr>
<tr>
<td>EDD, mm</td>
<td>7.27 ±0.49</td>
<td>7.25 ±0.70</td>
<td>0.900</td>
</tr>
<tr>
<td>ESD, mm</td>
<td>4.53 ±0.56</td>
<td>4.43 ±0.79</td>
<td>0.82</td>
</tr>
<tr>
<td>E/A</td>
<td>1.86 ±0.28</td>
<td>1.52 ±0.42</td>
<td>0.008</td>
</tr>
<tr>
<td>E/E’</td>
<td>19.26 ±4.12</td>
<td>23.79 ±7.09*</td>
<td>0.077</td>
</tr>
<tr>
<td>*LV mass, g</td>
<td>0.83 ±0.14</td>
<td>1.10 ±0.16</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are means±SDs; BP, blood pressure measured in conscious rats by noninvasive tail-cuff method; HR, heart rate; EF, ejection fraction; SWT, end-diastolic wall thickness of interventricular septum; PWT, end-diastolic wall thickness of posterior wall; EDD, end-diastolic dimension; ESD, end systolic dimension; E/A, mitral inflow E-A ratio, E/E’, mitral inflow E-septal tissue Doppler velocity E’ ratio; *LV mass was estimated in vivo by echocardiography.
### Evidence of heart failure at 21 weeks of age in rats fed with high salt diet

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low salt diet (n=6)</th>
<th>High salt diet (n=26)</th>
<th>Statin-treated group (n=13)</th>
<th>Control group (n=13)</th>
<th>P Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min*</td>
<td>211.5 ± 31.8</td>
<td>223.5 ± 36.5</td>
<td>221.9 ± 22.8</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure*, mmHg</td>
<td>97.9 ± 12.9</td>
<td>124.9 ± 12.0</td>
<td></td>
<td></td>
<td>121.2 ± 24.5</td>
</tr>
<tr>
<td>LV EF, %†</td>
<td>65.8±4.0</td>
<td>75.1 ± 74.3</td>
<td>74.3 ± 7.8</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>LVEDP, mmHg†</td>
<td>11.8 ± 2.1</td>
<td>16.8 ± 7.8</td>
<td></td>
<td></td>
<td>15.4 ± 4.9</td>
</tr>
<tr>
<td>BW, g</td>
<td>416.8 ± 223.9</td>
<td>375.7 ± 28.5</td>
<td></td>
<td></td>
<td>382.9 ± 35.5</td>
</tr>
<tr>
<td>Heart, g‡</td>
<td>1.20 ± 0.12</td>
<td>1.46 ± 0.09</td>
<td></td>
<td></td>
<td>1.46 ± 1.26</td>
</tr>
<tr>
<td>Lung, g‡</td>
<td>1.75 ± 0.11</td>
<td>1.84 ± 0.19</td>
<td>1.79 ± 0.26</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Heart/BW, mg/g</td>
<td>2.87 ± 0.25</td>
<td>3.91 ±0.41</td>
<td></td>
<td></td>
<td>3.83 ± 0.51</td>
</tr>
<tr>
<td>Lung/BW, mg/g</td>
<td>4.19 ± 0.33</td>
<td>4.93 ±0.66</td>
<td></td>
<td></td>
<td>4.68 ± 0.70</td>
</tr>
</tbody>
</table>

Values area means ± SD; HR, heart rate; LV EF, LV ejection fraction; LV EDP, LV end diastolic pressure; BW, body weight. *blood pressure and heart rate were measured from femoral arterial line by invasive method under anesthesia. †LV EF and LVEDP were measured by conductance catheter. ‡ Postmortem pathologic analysis. § P value from comparison between low salt diet and high salt diet groups. || P value < 0.05, when compared to low salt diet group
### S3. Lipid level at 21 weeks of age

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group (n=13)</th>
<th>Statin Treatment Group (n=13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Cholesterol, mg/dL</td>
<td>61.3 ± 16.6</td>
<td>60.8 ± 19.3</td>
<td>0.94</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>122.2 ± 30.1</td>
<td>116.7 ± 48.7</td>
<td>0.77</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>33.4 ± 9.2</td>
<td>31.3 ± 9.5</td>
<td>0.61</td>
</tr>
</tbody>
</table>

T-cholesterol, total cholesterol; HDL, high-density lipoprotein