Effects of Rosuvastatin vs. Simvastatin/ezetimibe on Arterial Wall Stiffness in Patients with Coronary Artery Disease

Ban Liu¹, Wenliang Che¹, Hongwei Yan², Weidong Zhu² and Hongbao Wang³

Abstract

Objective Statins prevent cardiovascular events in patients with coronary artery disease (CAD). However, there is little information regarding the vascular effects of statins on arterial wall stiffness in CAD patients.

Methods A total of 36 patients were randomly assigned to receive rosuvastatin (10 mg per day) or simvastatin/ezetimibe (10/10 mg per day) for eight weeks. The aim of the present study was to determine the effects of rosuvastatin or simvastatin/ezetimibe on arterial wall stiffness measured according to the brachial and ankle pulse wave velocity (baPWV) in CAD patients.

Results Both treatments significantly improved the levels of total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hs-CRP) (p<0.05). The ROCK activity and baPWV were significantly improved in the rosuvastatin group compared with that observed in the simvastatin/ezetimibe group (p<0.05). The changes in baPWV were significantly correlated with the changes in the ROCK activity (r=0.488, p<0.01), but not with the changes in the lipid profile or the hs-CRP level.

Conclusion Compared with simvastatin/ezetimibe (10/10 mg), rosuvastatin (10 mg) appears to more effectively improve arterial wall stiffness that may be mediated by modulation of the ROCK activity.

Key words: statin, low-density lipoprotein cholesterol, coronary artery disease, pulse wave velocity, ROCK activity

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Introduction

A relationship between the serum levels of low-density lipoprotein cholesterol (LDL-C) and the incidence of coronary artery disease (CAD) has been demonstrated (1, 2). Statins, which are inhibitors of 3-hydroxy-methylglutaryl co-enzyme A (HMG-CoA), can reduce the LDL-C level and are an established therapy in the primary and secondary prevention of CAD (3, 4). The overall benefits observed with statins are mediated not only by their cholesterol-lowering effects, but also by their pleiotropic anti-inflammatory effects (5). Cumulative evidence suggests that the ROCK pathway is involved in many steps of the inflammatory atherosclerotic process (6-8). Inhibition of the ROCK activity with Y-27632 limits early atherosclerotic plaque development in LDLr⁻/⁻ mice fed a high-cholesterol diet (9). The purpose of the present study was to determine the pleiotropic effects of statins on arterial wall stiffness and the correlations between arterial wall stiffness and inflammatory markers in patients with CAD.

Materials and Methods

Study design

This study involved Chinese patients with 50% or more stenosis in at least one major coronary artery who were referred for coronary angiography. The patients were randomized to receive eight weeks of rosuvastatin (10 mg per day)
or simvastatin/ezetimibe (10/10 mg per day). Rosuvastatin was chosen because it has been proven to be the most effective hydrophilic statin in lowering cholesterol (10). Rosuvastatin (10 mg/day) and simvastatin/ezetimibe (10/10 mg) are considered to equally decrease the LDL-C level (11). A total of 36 CAD patients with 50% or more stenosis in at least one major coronary artery were divided into a rosuvastatin (n=18) and simvastatin/ezetimibe (n=18) group at random. Rosuvastatin was administered at a dose of 10 mg/day and simvastatin/ezetimibe was administered at a dose of 10 mg/day in order to lower the LDL-C level without the use of any other lipid-lowering drugs. Patients with acute myocardial infarction (AMI), spastic angina pectoris, chronic diseases of the liver or kidney (a serum creatinine level of > 2.0 mg/dL or elevation of the alanine transaminase level exceeding three times the upper limit of normal), anemia, neurological or endocrine diseases or malignancy were excluded. No subjects had taken any statins before this study. All subjects were advised to continue their current medications and lifestyle for the duration of the study.

**Measurement of the lipid profiles, hsCRP levels and ROCK activity**

Blood samples were collected in citrate-treated tubes two times in all patients: 1) immediately before coronary angiography after an overnight fast and 2) after eight weeks of lipid-lowering treatment. The concentrations of high-sensitivity C-reactive protein (hsCRP) were measured using an immunoturbidimetric assay on a modular system random-access analyzer (Dade Behring, Deerfield, IL, USA).

To evaluate the ROCK activity, the Rho kinase-dependent phosphorylation of the myosin binding subunit (MBS) at threonine 853 (phospho-Thr853-MBS) was assayed in peripheral blood leukocytes, as previously described (12). The blood was collected at room temperature in heparinized tubes (20 U/mL). The leukocytes were isolated from the peripheral blood samples (15 mL), suspended and diluted, as previously described (13). After the proteins were precipitated, a Western blot analysis was performed, as previously described (13). The ROCK activity was expressed as the ratio of phospho-Thr853-MBS/total MBS normalized to the positive controls.

**Measurement of baPWV**

The patients were examined using a volume plethysmographic instrument (PWV/ABI; Colin Co, Komaki, Japan) in the morning following an overnight fast at the time of enrollment and at end of the study. The brachial and ankle pulse wave velocity (baPWV) was measured after allowing the patient to rest in the supine position for 10 minutes in a 24-26°C air conditioned room. The baPWV was calculated using a time-phase analysis of the right brachial artery pressure and volume waveforms at both ankles at the beginning of the study, and a repeated analysis was performed on the same side in each patient during the study (14).

**Table 1. Patients’ Characteristic**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Simvastatin/ezetimibe (n=18)</th>
<th>Rosuvastatin (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>65±13</td>
<td>67±18</td>
</tr>
<tr>
<td>Male(%)</td>
<td>11(61.1)</td>
<td>10(55.6)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3±3.1</td>
<td>25.1±3.5</td>
</tr>
<tr>
<td>Waist circumstance (cm)</td>
<td>96.1±4.7</td>
<td>96.0±4.7</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.95±0.2</td>
<td>4.01±0.17</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.42±0.28</td>
<td>1.43±0.29</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.11±0.08</td>
<td>1.10±0.12</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.40±0.10</td>
<td>2.42±0.15</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>2.0±0.38</td>
<td>2.1±0.35</td>
</tr>
<tr>
<td>Multi vessel disease, n(%)</td>
<td>9(50)</td>
<td>9(50)</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>12(66.7)</td>
<td>11(61.1)</td>
</tr>
<tr>
<td>Diabetes, n(%)</td>
<td>11(61.1)</td>
<td>12(66.7)</td>
</tr>
<tr>
<td>Smoking, n(%)</td>
<td>6(33.3)</td>
<td>6(33.3)</td>
</tr>
<tr>
<td>ROCK activity, %</td>
<td>83.2</td>
<td>86.1</td>
</tr>
<tr>
<td>baPWV (cm/s)</td>
<td>1769±421</td>
<td>1772±430</td>
</tr>
</tbody>
</table>

HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, hsCRP: high-sensitivity C-reactive protein, baPWV: brachial and ankle pulse wave velocity. No differences were observed among the 2 treatment groups (all p>0.05).

**Statistical analysis**

All statistical analyses were conducted using the Statistical Package for Social Sciences version 17.0 software package (SPSS Inc., Chicago, IL). The baseline characteristics of the two groups were analyzed using Student’s t-test or the Mann-Whitney U test for continuous variables and the chi-square for discrete variables. Paired Student’s t-test or the Wilcoxon test was performed to analyze the effects of the 8-week rosuvastatin or simvastatin/ezetimibe treatment. The Pearson correlation test was used to analyze the correlation between changes in baPWV and the other parameters. The data were expressed as the mean ± standard deviation (SD) or median, and p<0.05 was considered to be statistically significant.

**Results**

**Patient characteristics**

The baseline characteristics of the patients are summarized in Table 1. The patients in both treatment groups were matched for age, gender and cardiac risk factors (p>0.05).

**Changes in the lipid profiles, hsCRP levels and ROCK activity**

The patients in both groups had similar lipid profiles and hsCRP levels at randomization (Table 1). Both treatments produced similar reductions in the total cholesterol (TC), triglyceride (TG) and LDL-C levels compared to the baseline values (both p<0.05). Both treatments increased the high-density lipoprotein cholesterol (HDL-C) levels slightly compared with the baseline values; however, no statistical significance was observed (p>0.05) (Table 2). Both treatments...
Table 2. Effects of Treatment on Lipid Profiles, hsCRP, and baPWV

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin/ezetimibe day0</th>
<th>Simvastatin/ezetimibe day56</th>
<th>Rosuvastin day0</th>
<th>Rosuvastin day56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.95±0.25</td>
<td>2.20±0.32*</td>
<td>4.01±0.17</td>
<td>1.87±0.28*</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.42±0.28</td>
<td>1.20±0.22*</td>
<td>1.43±0.29</td>
<td>1.21±0.23*</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.11±0.08</td>
<td>1.13±0.08</td>
<td>1.10±0.12</td>
<td>1.15±0.10</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.40±0.10</td>
<td>1.43±0.17*</td>
<td>2.42±0.15</td>
<td>1.33±0.19*</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>1.68±0.38</td>
<td>1.02±0.28**</td>
<td>1.72±0.35</td>
<td>0.98±0.25**</td>
</tr>
<tr>
<td>baPWV (cm/s)</td>
<td>1,769±421</td>
<td>1,722±386</td>
<td>1,772±430</td>
<td>1,603±398†</td>
</tr>
</tbody>
</table>

HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, hsCRP: high-sensitivity C-reactive protein, baPWV: brachial and ankle pulse wave velocity.

* p<0.05 indicates comparison of measured values before and after 8-week treatment within individual group.

** p<0.01 indicates comparison of measured values before and after 8-week treatment within individual group.

† indicates difference between the simvastatin/ezetimibe 10/10mg vs. rosuvastatin 10mg group.

Table 3. Correlations between Changes in baPWV and Changes in Lipid and Inflammation Parameters

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>0.106</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.089</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.168</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>-0.172</td>
<td>NS</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>0.263</td>
<td>NS</td>
</tr>
<tr>
<td>ROCK Activity(%)</td>
<td>0.488</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, hsCRP: high-sensitivity C-reactive protein, baPWV: brachial and ankle pulse wave velocity, NS: not significant

Changes in baPWV

The baseline baPWV values were not different between the two treatment groups (Table 1). Rosuvastatin significantly decreased the baPWV values (p<0.05), while simvastatin/ezetimibe did not (p>0.05) (Table 2).

Correlations between the metabolic parameters, hsCRP levels, ROCK activity and baPWV values

No correlations were found between the changes in the LDL-C levels and the changes in the ROCK activity (r=0.197, p>0.05). We further analyzed whether any correlations existed between the changes in the baPWV values, lipid profiles, hsCRP levels or ROCK activity in the two treatment groups. No correlations were found between the changes in the baPWV values and the changes in the total cholesterol, triglyceride, LDL-C, HDL-C or hsCRP levels in either group (p>0.05). However, a strong association was observed between the changes in the baPWV values and the changes in the ROCK activity (r=0.488, p<0.01) in the subjects receiving rosuvastatin and simvastatin/ezetimibe (Table 3).

Discussion

In this randomized controlled study, we found that both rosuvastatin (10 mg) and simvastatin/ezetimibe (10/10 mg) similarly reduced the LDL-C, TC, TG and hsCRP levels after eight weeks. The PWV values are significantly decreased after 4-12 weeks of statin treatment (15, 16). The results of this study also demonstrate that rosuvastatin significantly...
ameliorated arterial wall stiffness after eight weeks of treatment in correlation with a reduced ROCK activity in the patients with CAD. Although rosuvastatin (10 mg) and simvastatin/ezetimibe (10/10 mg) have comparable lipid-lowering effects, only the rosuvastatin group achieved a significant improvement in arterial stiffness and inhibition of the ROCK activity, compared with that observed in the simvastatin/ezetimibe group.

Increased arterial stiffness is thought to act as a risk factor for cardiovascular events via an impaired coronary blood flow, direct atherogenic actions, increased cardiac afterload and microvascular damage (17-19). Epidemiologic and clinical studies have shown that measuring the PWV is the “gold standard” for assessing impaired aortic stiffness, and reducing the PWV levels is potentially beneficial in the management of patients with CAD (2, 4). BaPWV measurement is a simple and effective tool in clinical practice (20). The benefits of statin therapy extend beyond lipid-lowering effects (21). The “pleiotropic” effects of statins suggest that the improvements in outcomes are related as much to the anti-inflammatory actions as to the LDL-C-lowering effects of the drugs (5). Inflammatory responses in the vascular wall are thought to stiffen the arteries, both functionally and structurally (22). Considerable evidence suggests that the CRP level is an independent predictor of future cardiovascular events; however, the direct involvement of CRP in atherosclerosis remains controversial (21, 23). Data from the 1999-2000 National Health and Nutrition Examination Survey (NHANES) indicated that 47.1% of respondents 20 years of age or older had a high CRP level (24). Approximately one-third of the population has a CRP level above 3 mg/L (25).

Studies have demonstrated that ROCK is a critical contributor to many steps of the inflammatory atherosclerotic process (6-8). Treatment with the ROCK inhibitor fasudil causes a decrease in arterial intima media thickness, maximum flow velocity and macrophage accumulation in atherosclerotic lesions (26). Statins prevent the synthesis of important isoprenoid intermediates of the cholesterol biosynthetic pathway that serve as important lipid attachments for the posttranslational modification of small GTPases, such as Rho, Ras and Rac (27). By inhibiting mevalonate synthesis, statins prevent the membrane targeting of Rho and its downstream effector ROCK (27). It is difficult to separate the cholesterol-lowering effects of statins from their pleiotropic effects. Ezetimibe, which inhibits intestinal cholesterol absorption, was introduced in this study. Treatment with ezetimibe combined with a statin did not alter the progression of carotid artery intima-media thickening, despite a further reduction in the LDL-C and hsCRP levels, compared with that achieved with statins alone (28). Despite achieving equivalent reductions in the LDL-C and hsCRP levels with both treatments, rosuvastatin, not simvastatin/ezetimibe, was shown to improve arterial wall stiffness and reduce the ROCK activity in the present study. Our data also indicate that the ROCK activity may provide further predictive information regarding arterial wall stiffness in patients with CAD. In this study, we found that the hsCRP level is not the best predictor of vascular stiffness. We also found no significant correlations between arterial wall stiffness assessed according to the baPWV and aging, obesity, diabetes mellitus, hypertension and lipid profile abnormalities.

Several limitations remain in this study. This study was a single-center study with a small number of patients. A placebo group was not included due to the ethical implications of withdrawing statin therapy in patients with CAD. Statins may exert their anti-inflammatory effects via the Ras superfamily of small GTPases, including Ras, Rac and Cdc-42, which may also play a role in mediating vascular abnormalities (29). This study did not assess the effects of rosuvastatin on other members of the Ras superfamily. The mechanism underlying the improvement of arterial stiffness due to the inhibition of the ROCK activity by rosuvastatin is intriguing and requires further study.

**Conclusion**

This study demonstrates that rosuvastatin inhibits the ROCK activity in patients with CAD, independent of cholesterol reduction, and that rosuvastatin therapy has significant vascular benefits, likely due to the suppression of the ROCK pathway in the arterial wall.

**The authors state that they have no Conflict of Interest (COI).**

Ban Liu, Wenliang Che, and Hongwei Yan contributed equally to this work.

**References**


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