Hypertension is a major public health concern because it increases the risk of stroke, myocardial infarction, and congestive heart failure. Despite improved treatment modalities, a substantial number of patients with hypertension are refractory to medical intervention. Apart from well-known mechanisms that explain refractory hypertension, another potential contributing mechanism may be augmented sympathetic activity. Several studies have shown that, despite adequate blood-pressure (BP)-lowering therapy, the increased central sympathetic tone persists. Maybe more importantly, it has been suggested that increased sympathetic activity itself may play an additional pathophysiological role in the development of cardiovascular complications. We hypothesized that, as sympathoexcitation is a clear feature of primary hypertension, administration of a statin to hypertensive patients will reduce sympathetic nervous system activity.

**Background:** Experimental animal data suggest that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) might reduce enhanced sympathetic activity, a hallmark of hypertensive patients. This hypothesis was tested for the first time in patients with primary hypertension.

**Methods and Results:** Using a prospective, randomized, placebo-controlled, double-blind, cross-over design, a proof-of-principle trial was performed in 13 patients with mild to moderate hypertension, who were randomly assigned to a regimen of atorvastatin (80 mg/day) for 3 weeks, followed by placebo for 3 weeks or to a regimen of placebo for 3 weeks, followed by atorvastatin (80 mg/day) for 3 weeks. Microneurography was used at the end of each treatment period to measure sympathetic nervous system activity (muscle sympathetic nerve activity: MSNA). Heart rate variability (HRV) and plasma norepinephrine concentrations were also measured. Additionally, effects on blood pressure (BP) and heart rate (HR) were assessed by 24-h ambulatory BP measurement. Atorvastatin reduced postganglionic MSNA (atorvastatin 35.0±2.0 vs placebo: 39.2±1.5 bursts/min, P=0.008) and heart frequency corrected MSNA (atorvastatin: 58.5±2.0 vs placebo: 64.7±3.0 bursts/100 beats, P=0.02). Atorvastatin had no significant effect on plasma norepinephrine levels, HRV, BP or HR.

**Conclusions:** In patients with mild to moderate hypertension, atorvastatin reduces postganglionic MSNA, which supports the hypothesis that HMG-CoA reductase plays a role in sympathetic nervous system activity. (Circ J 2010; 74: 2622–2626)

**Key Words:** Hypertension; Statins; Sympathetic nervous system
**Methods**

**Participants**
We included 13 patients with primary hypertension who were a proof-of-principle trial. Inclusion criteria were: age 18–70 years, a body mass index (BMI) 18–35 kg/m², and a history of mild to moderate hypertension (defined as average awake SBP between 140 and 179 mmHg, or diastolic BP between 90 and 109 mmHg). Secondary hypertension was excluded according to standard clinical criteria. Informed consent was given by all patients prior to participation in the study.

**Study Protocol**
Using a prospective, double-blind, cross-over design, patients were randomly assigned to a regimen of atorvastatin (80 mg/day) for 3 weeks, followed by placebo for 3 weeks or to a regimen of placebo for 3 weeks, followed by atorvastatin (80 mg/day) for 3 weeks. If patients were already using statins, they were included in the study after a washout period of 2 weeks (n=4). At the end of each treatment period (atorvastatin or placebo) measurements were performed. Muscle sympathetic nervous system activity (MSNA) was assessed by microneurography of the peroneal nerve. In addition, heart rate variability (HRV) and venous plasma catecholamine concentrations were determined. Prior to each visit, ambulatory 24-h BP monitoring was performed. Experiments were conducted at 8:00 AM after an overnight (10-h) fast and with the patient lying supine in a quiet temperature-controlled room (23–24°C). Subjects had to abstain from caffeine, tea, alcohol, chocolates and smoking for at least 12 h prior to the test procedure. All experiments were carried out and examined by the investigator to identify and exclude noise artefacts. Microneurography recordings were quantified as bursts per minute, which has a high intra-individual reproducibility, and bursts per minute.

**Laboratory Determinations**
Fasting total cholesterol (TC), high-density lipoprotein (HDL) and triglyceride (TG) levels were measured at the end of each treatment period by automated enzymatic methods. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. For detecting potential statin side-effects, plasma liver enzymes and creatine kinase levels were measured at each visit (baseline, 3 and 6 weeks).

**HRV**
Using a 2-channel Holter (Medilog 4500-3, Oxford Instruments Ltd, UK) a 10-min ECG was recorded for each patient at each visit. Ectopic beats and arrhythmias were excluded using the Oxford scanning software (version 6.0). R–R interval selection was performed using a beat-to-beat filter set at N-N-N, whereby the interval being considered should start and end in a “normal” beat and so should the preceding R–R interval. Rejected intervals were interpolated over the invalid area. Before converting the interval tachogram to frequency domain analyses, the mean R–R interval was calculated from the tachogram and subtracted from each R–R interval to reduce spectral leakage. A fast Fourier transformation was performed from the interpolated tachogram resampled at 292 ms, using the Oxford spectral analysis software package. Results from the 10-min interval were averaged to form a composite spectrum. Total power between 0.003 and 0.40 Hz was calculated to represent the total variance for a 10-min interval. Power was quantified as total power, high frequency (HF; 0.15–0.40 Hz) and low frequency (LF; 0.04–0.15 Hz). HF represents the parasympathetic contribution to the spectrum, whereas LF represents a combination of parasympathetic and sympathetic influences. The LF/HF ratio is a measure of autonomic balance, with an increasing ratio representing sympathetic predominance.

**24-h Ambulatory BP Measurement**
Prior to each experiment, a validated 24-h indirect BP monitor (Mobil-O-Graph CE0434, Firmware version 12, I.E.M.)
Industrielle Entwicklung Medizintechnik GmbH, Stolberg, Germany) was connected to each patient.

Statistical Analysis
Data are expressed as mean±SEM unless indicated otherwise. Differences between measurements performed during atorvastatin administration or placebo were assessed using parametric (Student’s t-test for paired observations) or non-parametric (paired Wilcoxon) tests as appropriate. A power calculation assuming a basal sympathetic activity of 60±15 bursts/100 beats, revealed that in order to detect a difference of 25% in burst frequency with a power of 80% at a significance level of 0.05 (α), 11 subjects needed to be included. Allowing for a dropout and failure rate of micro-neurography of 20%, 13 patients needed to be included. A 2-tailed P-value <0.05 was considered to be statistically significant. Correlations between parameters were calculated using Pearson correlation coefficients.

Results
Table 1 presents the baseline characteristics of the study population. At entry, 10 of the 13 patients had BP >130 mmHg systolic or 80 mmHg diastolic. Only 1 patient was not on antihypertensive medication. The baseline medications remained unchanged throughout the course of the study. All patients completed the study but in 1 patient a MSNA measurement failed because of technical problems, so paired MSNA recordings were available in 12 of the 13 patients. There were no significant differences in the baseline characteristics of the groups of patients with regard to the sequence of atorvastatin or placebo.

Atorvastatin reduced the plasma TC and LDL-C levels in all patients (TC: from 5.4±0.3 to 3.5±0.2 mmol/L, P<0.001; LDL cholesterol: from 3.3±0.3 to 1.7±0.2 mmol/L, P<0.001). The HDL-cholesterol and TG levels were not significantly altered.

MSNA was significantly lower during atorvastatin 80mg compared with placebo (Figure 1) (total MSNA, atorvastatin: 35.0±2.0 vs placebo: 39.2±1.5 bursts/100 beats, P=0.008; frequency-corrected MSNA: atorvastatin: 58.5±2.0 vs placebo: 64.7±3.0 bursts/min, P=0.02). Although the MSNA values positively correlated with plasma cholesterol levels (all measurements combined, r=0.50, P=0.01, Figure 2), the reduction in MSNA was independent of the degree of change in plasma cholesterol levels (r=0.24, P=0.45) and did not correlate with the change in LDL-C levels (r=−0.22, P=0.51). This finding suggests that the effect was caused by atorvastatin itself, instead of the change in cholesterol level. The atorvastatin effect on MSNA was independent of baseline BP,

![Figure 1](image1.png)

![Figure 2](image2.png)
heart rate (HR), age and BMI. Plasma concentrations of norepinephrine (atorvastatin: 2.7±0.4 vs placebo: 2.4±0.2 nmol/L) and epinephrine (atorvastatin: 0.16±0.03 vs placebo: 0.15±0.03 nmol/L) were similar during atorvastatin and during placebo. Day-time and night-time systolic and diastolic BPs, as assessed by 24-h ambulatory BP measurement, were not significantly different between atorvastatin and placebo (Table 2). There was no difference in HRV between atorvastatin and placebo (Table 3).

Table 2. 24-h Ambulatory BP During Atorvastatin and Placebo Administration to Patients With Primary Hypertension

<table>
<thead>
<tr>
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<th>Atorvastatin</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>BP</strong></td>
<td>Day</td>
<td>Night</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>139±3</td>
<td>130±4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>89±3</td>
<td>83±4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>105±3</td>
<td>98±4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>81±5</td>
<td>68±5</td>
</tr>
</tbody>
</table>

Data are mean±SEM. MAP, mean arterial BP. Other abbreviations see in Table 1.

Table 3. HR Variability During Atorvastatin and Placebo Administration to Patients With Primary Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRV</strong></td>
<td>Day</td>
<td>Night</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>1,480±736</td>
<td>1,513±729</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>711±248</td>
<td>532±136</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.8±0.37</td>
<td>2.97±0.97</td>
</tr>
<tr>
<td>Total PSD (ms²)</td>
<td>5,090±1,473</td>
<td>4,579±1,830</td>
</tr>
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</table>

LF, low-frequency power; HF, high-frequency power; LF/HF, low-frequency/high-frequency ratio; PSD, power spectral density. Other abbreviation see in Table 1.

The results of this study provide evidence that a high dose of atorvastatin produces a significant reduction in post-ganglionic sympathetic nerve activity in patients with primary hypertension. Our conclusion is based on the finding of a nearly 9% lower MSNA with atorvastatin treatment compared with placebo. The lower MSNA levels did not translate into lower venous plasma norepinephrine levels or lower BP, or in a change in HRV.

The reduction in MSNA seemed to be related to the use of atorvastatin and not to the reduction in plasma cholesterol, but our study is too small to draw conclusions on this point.

The results of the present study are in line with earlier findings in animal experimental models. Kishi et al observed a significant reduction in 24-h urinary norepinephrine concentrations after treating stroke-prone spontaneous hypertensive rats for 30 days with atorvastatin. Several studies have shown that statins are able to significantly reduce BP, or in a change in HRV. The finding that the reduction in MSNA after administering atorvastatin 80 mg was not translated into a change in plasma norepinephrine levels is not completely unexpected. First, the plasma norepinephrine level is a global marker of noradrenergic sympathetic tone. The plasma norepinephrine level is the net result of neuronal release and clearance of norepinephrine, so it is possible that a reduced neuronal release of norepinephrine is masked if there is also a reduced clearance. An alternative explanation is that the MSNA results refer only to sympathetic activity in the skeletal muscle compartment whereas the plasma norepinephrine level is the result of all vascular beds. Indeed, it is well established that there are significant regional differences in sympathetic activity. Finally, there might be a dose–effect relationship for the effect of statins on plasma norepinephrine levels and this explanation is supported by a previous study in animals.

In rabbits with pacing-induced chronic heart failure (CHF), plasma norepinephrine levels were only reduced when administering a simvastatin dose up to 3 mg·kg⁻¹·day⁻¹, whereas the effects on MSNA were already found at much lower doses. The 3 mg·kg⁻¹·day⁻¹ dose in rabbits exceeds by far the usual dose (eg, simvastatin 40 mg once daily) in human subjects.

Several studies have shown that statins are able to significantly reduce BP in hypertensive patients. There are several possible reasons why this effect did not occur in the current study. First, the sympathoinhibitory effect of the dose of atorvastatin might not have been large enough to be translated into a significant decrease in BP or HR. Even a simvastatin dose as high as 3 mg·kg⁻¹·day⁻¹ did not affect the hemodynamics in the CHF rabbits, although RSNA was reduced. In accordance with the findings from that animal study and our current study, atorvastatin 80 mg administered to CAD patients had no effect on BP, despite a significant reduction in plasma norepinephrine levels. Second, it is possible that our study population was not large enough to uncover a decrease in BP. In addition, our patients were only treated and observed for a short period of time. Therefore, our study cannot exclude that statins do reduce BP in the long term. Finally, noncompliance with statin administration might be an explanation but the decrease in plasma TC and LDL-C levels in all patients argues against this possibility.

Study Limitations

Several potential limitations should be discussed. All but 1 patient were on antihypertensive treatments. Although this might interfere with the statin, it is unlikely to have con-
founded the results because all patients remained on the same medications, during both atorvastatin and placebo administration. Our study encompasses a relatively small group of subjects, but because of the cross-over design it was adequately powered for the assessment of MSNA.

Although it is difficult to dissect the contribution of atorvastatin itself from the reduction in LDL-C to sympathoinhibition, there was no indication that the degree of reduction in LDL-C correlated with the MSNA effect, thus favouring but not proving a pleiotropic effect of atorvastatin.

It is too premature to state that the findings of the present study have clinical implications. Although the decrease in sympathetic activity did not result in a change in BP or nor-ephinephrine concentration, this does not mean that this finding has no clinical relevance. High sympathetic tone has been associated with insulin resistance, metabolic effects and reduced skeletal muscle perfusion. All of these effects are mainly a-adrenergic mediated and were not assessed in this study. Patients with hypertension frequently have increased plasma lipids and are treated with statins. If statins indeed lower sympathetic activity, this might, apart from their effects on plasma lipids, contribute to their beneficial cardiovascular effects in the long term.

In conclusion, the present study shows a small but significant reduction in sympathetic nerve traffic after short-term atorvastatin administration in patients with primary hypertension. Although these findings need confirmation in larger groups of patients, they do suggest an additional beneficial mechanism by which statins reduce cardiovascular complications.

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Disclosure
None for all authors.

References