Simvastatin reduces sympathetic outflow and augments endothelium-independent dilation in non-hyperlipidaemic primary hypertension

Cheri L McGowan, Hisayoshi Murai, Philip J Millar, Catherine F Notarius, Beverley L Morris, John S Floras

ABSTRACT

Abstract Objectives Previous reports, involving hypercholesterolaemic hypertensive subjects, that statins reduce muscle sympathetic nervous activity (MSNA) did not investigate potential neural sites of such sympathoinhibition or determine its consequences for endothelial function or insulin resistance. This study of hypertensive subjects with lower plasma cholesterol tested the hypotheses that lipophilic simvastatin would attenuate resting sympathoexcitation and augment baroreflex modulation of MSNA and heart rate (HR), flow-mediated vasodilation and insulin sensitivity.

Design Prospective, randomised, double-blind, placebo-controlled crossover study.

Setting Academic hospital-based study.

Patients Fourteen non-hyperlipidaemic primary hypertensive subjects (10 men; overall mean±SD age 58±12 years).

Interventions Four weeks of simvastatin (80 mg/day) or placebo.

Main outcome measures Resting blood pressure (BP), HR, MSNA, spontaneous arterial baroreflex MSNA and HR modulation, endothelium-dependent and endothelium-independent vasodilation, and the homeostatic model assessment of insulin resistance (HOMA-IR).

Results Simvastatin lowered MSNA burst frequency (from 32±12 to 25±9 bursts/min) and MSNA burst incidence (from 55±23% to 43±17%; all p<0.01) without affecting BP, HR, baroreflex modulation of either MSNA or HR, or HR variability (all p>0.05). Plasma glucose, insulin, HOMA-IR and endothelium-dependent vasodilation (all p>0.05) were unchanged, whereas endothelium-independent vasodilation increased (7.1±3.8% to 9.7±3.9%; n=13; p<0.01). The fall in MSNA was unrelated to the decrease in low-density lipoprotein cholesterol (r=0.41, p=0.14).

Conclusions These findings are consistent with the concept that, in non-hyperlipidaemic subjects with primary hypertension, simvastatin causes a cholesterol-independent reduction in an elevated central set-point for MSNA, without affecting arterial baroreflex modulation of either MSNA or HR. There may be less neurogenic constraint on endothelium-independent vasodilation as a consequence.

INTRODUCTION

Primary hypertension is characterised by both increased sympathetic nervous traffic to the heart, kidneys and skeletal muscle (muscle sympathetic nerve activity (MSNA))1 2 and decreased baroreflex heart rate (HR) modulation (baroreceptor sensitivity (BRS)).1 In experimental models of hypertension, these autonomic disturbances have been linked to an increased production of reactive oxygen species and NAD(P)H oxidase within brain centres involved in the generation or modulation of effenter sympathetic and parasympathetic nerve discharge, such as the rostral ventrolateral medulla and the nucleus tractus solitarius.4

In experimental models of hypertension and heart failure, lipophilic statins such as simvastatin and atorvastatin5 attenuate these autonomic disturbances, independently of any effects on cholesterol, by modifying within these and related brain regions signalling pathways involving G proteins, endothelial, neuronal and inducible NO synthase expression6 8 and angiotensin II type 1 (AT1) receptor and NAD(P)H oxidase subunit protein expression.5 9 10 In a normolipidaemic rabbit model of heart failure, simvastatin, 3 mg/kg/day for 3 weeks, diminished renal sympathetic nerve activity (RSNA), plasma norepinephrine concentrations and total peripheral resistance, and augmented tonic and reflex HR modulation and arterial baroreflex regulation of RSNA.9 10

In an uncontrolled study involving 10 hypercholesterolaemic hypertensive subjects, 8 weeks of atorvastatin was reported to decrease MSNA by 20% and to increase BRS.11 These authors subsequently allocated 31 hypercholesterolaemic hypertensive patients to receive either simvastatin (40 mg/day; n=15) or placebo (n=16). Simvastatin also decreased MSNA, by 24%, and increased BRS, but had no effect on blood pressure (BP).12 Using a placebo-controlled randomised crossover design, Gomes et al13 reported that 3 weeks of atorvastatin (80 mg/day) reduced MSNA of 13 primary hypertensive subjects (mean total cholesterol 5.4 mmol/l; four previously statin treated), by only 10%, and atorvastatin had no effect on HR or its variability, or on ambulatory BP. In a non-randomised study of treated hypertensive patients with chronic kidney disease, atorvastatin (20 mg/day) after 6 weeks reduced MSNA in 10 subjects by 29%, without affecting BP or HR.14 By contrast, in a randomised placebo-controlled protocol involving a non-ischaemic heart failure population without a clinical indication for statin therapy (n=18), 3 months of atorvastatin (10 mg/day) had no effect on MSNA,15 whereas in a crossover trial involving six such patients, 1 month of simvastatin (40 mg/day) reduced MSNA by 24%.16

None of these studies sought specifically to determine a site at which these lipophilic statins affected...
the regulation of MSNA in hypertension, or whether MSNA was reduced similarly in hypertensive subjects anticipated a priori to have increased central sympathetic outflow to skeletal muscle but lacking a contemporary clinical indication for cholesterol lowering. We therefore tested the hypotheses that, in otherwise healthy individuals with primary hypertension, 4 weeks of high-dose simvastatin would (1) lower resting MSNA and (2) augment arterial baroreflex modulation of MSNA and HR.

In addition, none of these recently published studies evaluated concurrently the vascular or metabolic consequences of such sympathoinhibition. Acute increases in MSNA can impair surrogates of endothelial function, such as flow-mediated dilatation, and it has been hypothesised that impaired endothelial function could itself increase MSNA. We therefore tested the secondary hypothesis that any reductions in MSNA with simvastatin would relate inversely to increases in flow-mediated vasodilation. Present concern that statins increase the risk of developing diabetes stimulated us to test also the hypothesis that any reduction in MSNA observed would be accompanied by less insulin resistance.

METHODS
Participants
Fourteen statin-naïve hypertensive but normcholesterolaemic, non-diabetic, non-smoking and otherwise healthy adult volunteers without chronic kidney disease participated in this study. Hypertension was defined as BP ≥140/90 mm Hg on three or more independent readings, or presentation with prior prescription of antihypertensive medication. Cardiovascular risk, as estimated by these participants’ primary or specialist physicians, was considered sufficiently low as not to warrant statin therapy. Potential participants with low-density lipoprotein cholesterol (LDL cholesterol) >4.5 mmol/l were excluded. The Research Ethics Boards of the University Health Network and Mount Sinai Hospital approved the protocol.

Study design
After giving written informed consent, participants were first familiarised with all experimental procedures, and then allocated according to a double-blind randomisation schedule by our pharmacy to either a statin-start group (80 mg daily) or a placebo-start group. For 4 weeks, one tablet was taken daily with the evening meal. After a washout period of at least 1 week, participants then ingested the other preparation daily with the evening meal. After a washout period of at least 10 min, after which venous blood was drawn for analysis in plasma of total cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, triglycerides, free fatty acids, glucose and insulin concentrations.

Laser Doppler flowmetry was then used to assess endothelium-dependent microvascular perfusion in skin (780 nm LDPM probe; Perilux PF Id; Perimed, Stockholm, Sweden). Measures were taken from the left forearm during 2 min of baseline, 3 min of proximal occlusion (>50 mm Hg above systolic BP), and 5 min of postocclusive reactive hyperaemia. After a 10 min stabilisation period, brachial artery diameter and velocity measurements were acquired using high-resolution B-mode and Doppler ultrasound (7–10 mHz linear array probe; Vivid 7; GE Healthcare, Pittsburgh, Pennsylvania, USA), respectively. The arm and transducer were stabilised, and a longitudinal section of the artery was scanned 2–5 cm above the elbow. After the optimal image was secured, a baseline was recorded over a 1 min period. To elicit NO-mediated endothelium-dependent vasodilation, post-ischaemic reactive hyperaemia was then induced by inflating a BP cuff (5 cm below the antecubital fossa) to 50 mm Hg above systolic BP for 5 min. Three minutes of data were then acquired after cuff release. To assess endothelium-independent smooth muscle responsiveness, sublingual nitroglycerine (400 µg; Sanofi Aventis, Laval, Quebec, Canada) was administered at least 15 min after hyperaemia. After a 1 min baseline, diameter and flow images were acquired for a further 5 min.

Data analysis
Continuously acquired data were digitised and stored with LabView (National Instruments, Austin, Texas, USA). Signal output was inscribed by a Gould Viper recorder (Gould Instrument Systems, Valley View, Ohio, USA), sampled at a frequency of 200 Hz (with the exception of the ECG: 1000 Hz), and, after conversion from analogue to digital format, stored on a PC desktop for subsequent offline analysis.

MSNA was quantified as burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats). Tonic control of HR (HR variability (HRV)) was assessed using fast Fourier transformation according to published methods. The following spectral bands were derived: very low frequency (PVLF), 0.0098–0.05 Hz; low frequency (PL), 0.05–0.15 Hz; and high frequency (PH), 0.15–0.50 Hz, with total power (PT) representing the sum of power within these three bands.

Arterial baroreceptor HR modulation (BRS) was estimated non-invasively using two complementary techniques. Spontaneous BRS was assessed using the systolic BP (stimulus) and R-R interval (response) sequence method (BRS<sub>seq</sub>), as applied previously in our laboratory. For each participant, all data acquired over the baseline rest were scanned to identify sequences of three or more cardiac cycles in which rises or falls in systolic BP were followed immediately by concordant changes in R-R interval. Values for all highly correlated (r > 0.85) R-R/ systolic BP relationships were averaged to determine the mean spontaneous BRS for each subject. Arterial baroreflex HR modulation was also estimated independently using spectral analysis by deriving the coherence and gain of the transfer function relating low-frequency variability of systolic BP (input variable) to low-frequency variability of R-R interval (output variable) (BRS<sub>lf</sub>). Arterial baroreflex modulation of sympathetic outflow to muscle, a primary outcome variable, was estimated
similarly but separately for the three prespecified frequency bands by deriving for each the coherence and gain of the transfer function relating variability of diastolic BP (input variable) to variability of MSNA (output variable).23

The change from baseline in skin blood–vascular perfusion was calculated as an independent index of cutaneous endothelium-dependent flow. With respect to brachial artery endothelium-dependent and endothelium-independent function assessments, all diameter images were sampled at end diastole and digitised and stored at 1 s intervals for offline analysis using commercially available semiautomated edge-detection software (Brachial Analyser; Medical Imaging Applications, Iowa City, Iowa, USA) by one blinded observer. Diameter was measured between the intima–lumen interface at the distal and proximal vessel wall. Resting diameters were calculated as the average of all images taken over the 1 min baseline. Relative flow-mediated dilation provided an index of endothelium-dependent vasodilation, and was calculated as percentage increase in brachial artery diameter from baseline to peak dilation.27 Peak shear stress ((4 × peak velocity)/diameter at peak velocity) was also calculated.28 To provide a measure of endothelium-independent vasodilation reflecting vascular smooth muscle function, the maximum response to nitroglycerine was calculated as the percentage increase from baseline diameter.26

Blood samples were assayed independently using standard techniques by Toronto Medical Laboratories (University Health Network, Toronto, Ontario, Canada). To ensure double-blinding, the results of these analyses were set aside and not released to the investigators until the entire study protocol and the analysis and closure of all study data were complete. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by the equation: HOMA-IR = (fasting plasma (insulin×glucose)/22.5)×100.49

### Statistical analysis

This study was powered to detect a change in the primary endpoint, MSNA burst frequency. A priori sample size calculations assuming a 20% reduction in MSNA in a crossover trial and with an assigned α of 0.05 and β 0.2 estimated a required sample of 11 patients. All data were recorded, analysed, confirmed and tabled with all investigators blinded to tablet allocation. Between-treatment (simvastatin vs placebo) differences were analysed using paired t tests or Wilcoxon signed-rank tests. Pearson correlation coefficients were used to assess associations between study parameters. All data were analysed using Sigma Stat for Windows (V3.5; Jandel Scientific Corp, San Rafeal, California, USA), and an α level of ≤0.05 was considered statistically significant. Values are presented as mean ±SD, unless otherwise stated.

### RESULTS

Participant characteristics appear in table 1. All participants completed the full protocol. The mean washout period between the two arms of the study was 17±11 days. Body weight was similar on the 2 study days (p>0.05). No adverse symptoms or laboratory indices were reported or detected. Three subjects exhibited arterial or venous ectopy during the placebo session; when they were taking simvastatin, the frequency of these complexes fell by 55%. Study order had no effect on any reported variable (p>0.05).

Simvastatin reduced both mean MSNA burst frequency and mean MSNA burst incidence, each by ~20% (both p<0.01; table 2, figure 1), but there were no significant differences between the 2 study days with respect to systolic BP or HR (both p>0.05). Diastolic BP tended to be lower after 4 weeks of simvastatin (p=0.055; table 2). As anticipated, simvastatin lowered both LDL cholesterol and total cholesterol (p<0.01; table 2), but these reductions were unrelated to the decrease in MSNA (r=0.41, p=0.14 and r=0.30, p=0.31, respectively).

No differences were observed between simvastatin and placebo with respect to the tonic or arterial baroreflex modulation of HR (all p>0.05), or for baroreflex modulation of MSNA within any frequency band (coherence, all p>0.05; transfer function gain, all p>0.35) (table 3).

MSNA on the placebo day was not related to either brachial artery (r =−0.24, p=0.41) or skin microcirculatory (r =−0.28, p=0.34) estimates of endothelial function. Brachial artery shear profiles did not differ between the 2 study days (p>0.05). Simvastatin had no effect on endothelium-dependent vasodilation of either the skin microcirculation or the brachial artery (p>0.05 for both; table 4), and there were no relationships between changes in MSNA and changes in either variable (r =−0.39, p=0.17 and r=0.25, p=0.39, respectively).

### Table 1  Participant characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±12</td>
</tr>
<tr>
<td>Male/Female</td>
<td>10/4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.74±0.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>94±31</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.3±6.7</td>
</tr>
</tbody>
</table>

### Table 2  Time domain haemodynamic, autonomic and metabolic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>139±15</td>
<td>137±11</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>81±10</td>
<td>77±8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>59±8</td>
<td>61±10</td>
</tr>
<tr>
<td>BRSSEQ (ms/mm Hg)</td>
<td>9.7±4.4</td>
<td>10.4±6.8</td>
</tr>
<tr>
<td>Muscle sympathetic nerve activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burst frequency (bursts/min)</td>
<td>32±12</td>
<td>25±9**</td>
</tr>
<tr>
<td>Burst incidence (bursts/100 heartbeats)</td>
<td>55±23</td>
<td>43±17**</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.8±0.9</td>
<td>3.2±0.8**</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mmol/l)</td>
<td>3.1±0.7</td>
<td>1.6±0.5**</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mmol/l)</td>
<td>1.2±0.4</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1±0.04</td>
<td>0.8±0.3*</td>
</tr>
<tr>
<td>Free fatty acids (μmol/l)</td>
<td>667±199</td>
<td>672±228</td>
</tr>
<tr>
<td>Insulin (μU/l)</td>
<td>3.4±2.5</td>
<td>4.0±4.6</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.2±0.3</td>
<td>5.3±0.6</td>
</tr>
<tr>
<td>Insulin resistance (HOMA-IR)</td>
<td>0.8±0.6</td>
<td>1.0±1.3</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SD. *p<0.05; **p<0.01 compared with placebo. BRSSEQ arterial baroreflex sensitivity for heart rate, assessed using the sequence method; HOMA-IR, homeostatic model assessment of insulin resistance.
Brachial artery endothelium-independent dilation was significantly greater on the simvastatin day (7.1±3.8% to 9.7±3.9%, n=13; p<0.01; figure 2; table 4). Absolute changes in endothelium-independent dilation were unrelated to absolute changes in MSNA burst frequency (r=−0.23, p=0.46).

No significant differences between simvastatin and placebo were observed for plasma insulin (p=0.73) or glucose (p=0.39), or the calculated HOMA-IR (p=0.84) (table 2), but there was a non-significant trend for reductions in MSNA with simvastatin to correlate with decreases in HOMA-IR (r=0.49, p=0.08).

**DISCUSSION**

In previous non-crossover and crossover studies—involving hypertensive patients requiring lipid-lowering therapy—atorvastatin or simvastatin reduced MSNA by 10–24%. The present randomised placebo-controlled crossover trial contributes to the current literature on this topic in several novel and important ways. First, it extends the population in whom this effect can be shown to occur to a lower-risk non-smoking, non-diabetic otherwise healthy primary hypertensive cohort not requiring statin therapy. The latter is an important consideration, because in a recently reported study involving patients with heart failure also without a clinical indication for lipid reduction (but who would be expected to have even greater resting sympathoexcitation), atorvastatin had no effect on MSNA. Second, all prior studies were limited in their focus to the MSNA end point. None examined the effect of these lipophilic statins (atorvastatin or simvastatin) on the arterial baroreflex regulation of MSNA.

**Figure 1** Individual average resting muscle sympathetic nerve activity burst frequency (left panel) and burst incidence (right panel) data, with their means and SDs, acquired after 4 weeks of placebo or simvastatin 80 mg/day.

**Table 3** Frequency domain indices

<table>
<thead>
<tr>
<th>Index</th>
<th>Placebo</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>185±120</td>
<td>313±537</td>
</tr>
<tr>
<td>P_h (ms²)</td>
<td>295±210</td>
<td>444±577</td>
</tr>
<tr>
<td>P_f (ms²)</td>
<td>1274±821</td>
<td>1542±1516</td>
</tr>
<tr>
<td>P_f/P_h (ms²)</td>
<td>2.6±2.7</td>
<td>3.6±5.6</td>
</tr>
<tr>
<td>Coherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P_L</td>
<td>0.47±0.3</td>
<td>0.52±0.2</td>
</tr>
<tr>
<td>BRS_L (ms/mm Hg)</td>
<td>6.80±5.6</td>
<td>6.15±1.8</td>
</tr>
<tr>
<td>MSNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P_L</td>
<td>0.28±0.2</td>
<td>0.31±0.2</td>
</tr>
<tr>
<td>P_f</td>
<td>0.36±0.3</td>
<td>0.35±0.2</td>
</tr>
<tr>
<td>P_h</td>
<td>0.27±0.2</td>
<td>0.26±0.2</td>
</tr>
<tr>
<td>Baroreflex transfer function gain</td>
<td>0.59±1.0</td>
<td>0.39±0.4</td>
</tr>
<tr>
<td>P_h (unit/mm Hg)</td>
<td>1.22±1.5</td>
<td>0.98±1.1</td>
</tr>
<tr>
<td>P_f (unit/mm Hg)</td>
<td>1.83±1.6</td>
<td>2.18±1.8</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SD. No comparisons are significant at p<0.05.

**Table 4** Vascular indices

<table>
<thead>
<tr>
<th>Index</th>
<th>Placebo</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting flow (AU)</td>
<td>8.4±3.3</td>
<td>10.8±9.3</td>
</tr>
<tr>
<td>Peak flow (AU)</td>
<td>30.6±19.1</td>
<td>31.7±24.7</td>
</tr>
<tr>
<td>Peak flow-resting flow change (%)</td>
<td>284.8±211.4</td>
<td>213.2±148.2</td>
</tr>
<tr>
<td>Endothelium-dependent dilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline diameter (mm)</td>
<td>4.8±0.9</td>
<td>4.7±0.7</td>
</tr>
<tr>
<td>Peak diameter (mm)</td>
<td>5.1±0.9</td>
<td>5.0±0.7</td>
</tr>
<tr>
<td>Flow-mediated dilation (%)</td>
<td>6.0±2.9</td>
<td>6.7±3.2</td>
</tr>
<tr>
<td>Endothelium-independent dilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline diameter (mm)</td>
<td>4.7±0.9</td>
<td>4.7±0.7</td>
</tr>
<tr>
<td>Peak diameter (mm)</td>
<td>5.1±0.8</td>
<td>5.2±0.7</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td>7.1±3.8</td>
<td>9.7±3.9*</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SD. *p<0.01 compared with placebo.

AU, arbitrary units.

The relative preservation of NO bioavailability in the placebo state as an anticipated consequence of the vascular health of subjects selected (recruitment being restricted to non-diabetic, non-smoking individuals lacking clinical indication for lipid-lowering therapy or chronic kidney disease); background therapy (11 of 14 participants were receiving chronically either ACE inhibition or angiotensin receptor blockade treatment, both of which can increase endothelium-dependent vasodilation31); and other potential mechanisms by which statin therapy might predispose to diabetes.20 In the only published investigation using a randomised placebo-controlled crossover study design and involving a similar cohort of normcholesterolaemic hypertensive participants, 2 weeks of fluvastatin had no effect on forearm blood flow responses to brachial artery infusion of acetylcholine, as a direct test of endothelium-dependent vasodilation32; MSNA was not recorded in that experiment.

In contrast, the observed decrease in MSNA was accompanied by an increase in nitrate-stimulated, endothelium-independent vasodilation. Similar observations have been made in statin-naive patients with acute coronary syndrome after 4 months of atorvastatin or pravastatin treatment33 and in patients with type 2 diabetes after 6 weeks of atorvastatin.34 The augmented responses to nitroglycerine documented in the present series may reflect less neurogenic constraint on the dilator capacity of vascular smooth muscle as a result of diminished MSNA. Indeed, in a recent experiment involving 10 healthy male volunteers submitted to a sympathoexcitatory stimulus, the brachial dilator response to nitroglycerine was augmented MSNA. Indeed, in a recent experiment involving 10 healthy male volunteers submitted to a sympathoexcitatory stimulus, the brachial dilator response to nitroglycerine was augmented by intravenous infusion of the centrally acting sympatholytic drug, clonidine.35 As baseline diameter was not increased, an inhibitory effect of simvastatin on vascular Rho kinase activity36 is less likely.

In the patients with heart failure studied by Horwich et al,15 atorvastatin also reduced LDL cholesterol by 37% relative to placebo but had no effect on MSNA, indicating that the observed reductions in MSNA with statins cannot be attributed to their lipid-lowering effect. Importantly, in both the prior study by Gomes et al13 and the present series, no relationships between statin-induced reductions in cholesterol and changes in MSNA could be discerned. The more likely mechanism is a reduction in central oxidative stress,16 which can be detected within 3 days of initiation of statin therapy, before any reduction in plasma lipids, as a consequence of blockade of the geranylgeranyl pyrophosphate pathway involved in activating Rac, Ras and Rho G-proteins.37 38

The mechanism by which statins might increase the risk of diabetes29 has yet to be established. However, there is substantial literature linking insulin resistance to activation of the sympathetic nervous system.21 A reflexively mediated increase in sympathetic vasoconstrictor tone has been shown to induce acute insulin resistance in the forearm of healthy volunteers, and a cross-sectional study involving obese normotensive subjects identified significant correlations between MSNA and HOMA-IR.40 Conversely, insulin sensitivity of insulin-resistant hypertensive subjects or patients with heart failure can be augmented if sympathetic vasoconstrictor tone is interrupted by α-adrenoceptor blockade,41 42 or diminished, by centrally acting agents43 44 or afferent renal denervation.45 Whether a similar reduction in central sympathetic outflow elicited by statin therapy also attenuates insulin resistance has yet to be reported. In the present series, no such relationship was identified. It may be that the change in MSNA did not result in a corresponding increase in skeletal muscle blood flow or in insulin-mediated glucose uptake (not quantified in the present series) or that any

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Figure 2  Endothelium-independent responses of individual subjects, and their means and SDs, acquired after 4 weeks of placebo or simvastatin 80 mg/day.
potential beneficial neural–metabolic interaction is offset by the induction of other, proglycaemic, effects of longer-term statin therapy.

CONCLUSIONS

Statins have achieved the status of being one of the most widely prescribed classes of medication as a result of their capacity to reduce cardiovascular morbidity and mortality in high-risk populations.46 This action has been attributed thus far primarily to the lowering of total and LDL cholesterol, with little attention directed at any concurrent autonomic effects, which may be both independent of changes in plasma cholesterol and a function of lipophilicity, permitting penetration of some statins into brain sites involved in neural regulation of the heart and circulation. Although BP did not fall, increased sympathetic outflow has also been linked to ventricular hypertrophy,47 insulin resistance,48 arrhythmias49 and premature mortality.50

In the present study, short-term high-dose simvastatin reduced sympathetic outflow in individuals with primary hypertension but without current clinical indication for lipid-lowering therapy, yet this lipophilic statin did not alter the baroreflex modulation of MSNA or that of HR or tonic HR modulation. These findings are consistent with a central neural or ganglionic sympathoinhibitory, rather than an afferent baroreceptor-mediated, site of action of simvastatin in this patient population. The lack of effect on HRV also excludes an afferent sympathoinhibitory, rather than an efferent, parasympathetic component.51

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