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ORIGINAL ARTICLE

Simvastatin reduces sympathetic activity in men with hypertension and hypercholesterolemia

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Beyond their hypolipidemic effect, statins reduce cardiovascular risk in hypertensive subjects via various mechanisms; one suggested mechanism is that they reduce sympathetic activity. We investigated the hypothesis that simvastatin decreased muscle sympathetic nerve activity (MSNA) in 31 hypertensive subjects with hypercholesterolemia (aged 38.7 ± 10 years). In this randomized, placebo-controlled, double-blinded study, patients were treated with simvastatin (40 mg day^{-1}; n=15) or placebo (n=16) for 8 weeks. Before and after treatment, we measured MSNA, blood pressure and heart rate. Baroreceptor control of the heart rate, or baroreceptor sensitivity (BRS), was computed by the sequence method, a cross-analysis of systolic blood pressure and the electrocardiogram R–R interval. Blood samples were tested for plasma levels of catecholamines, neuropeptide Y, aldosterone, endothelin and renin activity. Simvastatin significantly reduced MSNA (from 36.5 ± 5 to 27.8 ± 6 bursts per min, P=0.001), heart rate (from 77 ± 6.7 to 71 ± 6.1 beats per min, P=0.01) and both total and low-density lipoprotein cholesterol (from 249 ± 30.6 to 184 ± 28.3 mg dl^{-1}, P=0.001 and from 169 ± 30.6 to 117 ± 31.2 mg dl^{-1}, P=0.01, respectively). Simvastatin also improved BRS (from 10.3 ± 4.1 to 17.1 ± 4.3 ms per mm Hg, P=0.04). No changes were observed in systolic or diastolic blood pressures, or in plasma levels of catecholamines, neuropeptide Y, endothelin, aldosterone and renin activity. After simvastatin therapy, MSNA and BRS were inversely related (r=−0.94, P<0.05). In conclusion, we found that, in patients with hypertension and hypercholesterolemia, simvastatin reduced MSNA, and this was related to increased baroreceptor sensitivity.
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INTRODUCTION

The influence of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, or 'statins', on plasma lipid concentrations is well established.[1,2] Clinical effects of statins have been investigated in various groups of patients, particularly those with cardiovascular and metabolic disorders, in patients with low and high cardiovascular risks and in both primary and secondary preventions.[3–8] Many randomized, placebo-controlled studies have shown that, in patients with hypercholesterolemia, a reduction in plasma cholesterol with HMG-CoA reductase inhibitors was followed by substantial reductions in cardiovascular morbidity and mortality.[3–8] Furthermore, statins showed clinical efficacy in patients who did not have high cholesterol levels; this suggested that statins might exert beneficial effects in addition to their hypolipidemic actions.[8–10]

One cardioprotective mechanism of action may be related to statin's interactions with the neurohumoral system, particularly in the renin–angiotensin pathway and the sympathetic nervous system. Statin's sympathoinhibitory effects have been tested in both animal and human models. In normolipidemic rabbits with heart failure, simvastatin increased heart rate variability (HRV) and reduced sympathetic outflow.[11] In patients with hyperlipidemia, either with or without coronary artery disease, atorvastatin significantly improved the time and frequency domain indices of HRV; however, interestingly, post-therapeutic low-density lipoprotein (LDL) levels did not correlate with the indices of HRV.[11] Furthermore, a few studies in patients with heart failure showed that statins improved sympathovagal balance, as reflected in the change in HRV indices.[12,13] Statins are commonly prescribed for patients with hypertension, both with and without hypercholesterolemia, to reduce their cardiovascular risk. To date, no randomized, placebo-controlled studies have investigated whether statins can reduce sympathetic tone in subjects with hypertension, or ascertained the mechanisms involved.

The aim of this study was to conduct a randomized, placebo-controlled study on the influence of simvastatin on sympathetic activity in subjects with hypertension and hypercholesterolemia. Sympathetic activity was measured *in vivo* with microneurography.

METHODS

Subjects

We studied 31 men, aged 38.7 ± 10 years, with a mean body mass index of 28.0 ± 4 kg m^{-2}. The subjects had hypercholesterolemia, defined as fasting total

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Table 1 Characteristic of subjects in simvastatin and placebo group at baseline

	Simvastatin	*Placebo*	P-*value*
Number of patients	15	16	NS
Age (years)	39.0 ± 10.2	38.3 ± 10.1	NS
BMI (kg m^{-2})	28.7 ± 4.5	27.3 ± 4.1	NS
Blood pressure lowering medication, number of patients (% of total number)	10 (66.7%)	11 (68.75%)	NS
AT_1 receptor antagonists	3 (20.0%)	3 (18.7%)	NS
ACE inhibitors	4 (26.6%)	4 (25.0%)	NS
Calcium antagonists	1 (6.7 %)	1 (6.25 %)	NS
β-Blockers	2 (13.3%)	3 (18.7%)	NS
Diuretics	1 (6.7 %)	1 (6.25%)	NS

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; NS, nonsignificant.

and LDL cholesterol levels ⩾190 and ⩾115 mg dl^{-1}, respectively, and mild-to-moderate essential hypertension (blood pressures: 140–179/90–109 mm Hg). According to routine investigations and laboratory findings, other cardiovascular, metabolic, endocrine and neurological diseases were excluded. All subjects were screened to exclude central and peripheral neurological disorders. None of the subjects were currently using lipid-lowering drugs. Antihypertensive therapies, including angiotensin-converting enzyme inhibitor or β-adrenergic receptor inhibitor (β-blocker), remained unchanged for 3 months before and during the study (Table 1). Patients were prohibited from the chronic use of drugs that might potentially influence the nervous system. Active smokers and alcohol abusers were excluded from the study. The day before the experiment, subjects were asked not to drink alcohol, coffee or use other stimulants. Informed consent was obtained from all participants. The institutional review board of the Medical University of Warsaw approved the study protocol.

Study design

The study was double blinded, randomized and placebo controlled. Subjects were assigned to 40 mg of simvastatin (Simvasterol; Gedeon Richter Marketing Polska, Warsaw, Poland; n=15) or placebo (n=16). All recordings were performed twice: once before and once after 8 weeks of therapy. Recordings were performed in a calm investigation room after 30 min of supine rest. All subjects underwent recordings of muscle sympathetic nervous activity (MSNA), heart rate (HR) and continuous, non-invasive systolic and diastolic blood pressure (SBP and DBP, respectively). Blood samples were taken before each recording.

Measurements

HR was recorded continuously (Power Lab Data Acquisition System, AD Instruments, Colorado Springs, CO, USA). Blood pressure was measured with a digital photoplethysmograph device capable of providing accurate beat-to-beat systolic and diastolic values (Finapress, Ohmeda 2300, Monitoring Systems, Englewood, CO, USA). MSNA signals were obtained with the microneurography technique (Nerve traffic analysis system, University of Iowa, Iowa City, IA, USA).[14] Briefly, a recording electrode was placed into the peroneal nerve at the popliteal fossa, posterior to the fibular head, and a reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The nerve signals were amplified (gain 70 000–1 60 000), band-pass filtered (700–20 00 Hz), full-wave rectified and integrated with a resistance–capacitance circuit (time constant 0.1 s). The criteria for an adequate MSNA recording included: pulse synchrony; facilitation during the hypotensive phase of the Valsalva maneuver, and suppression during the hypertensive overshoot after release; and an increase in response to holding the breath.[14]

Baroreflex control of the HR, or baroreflex sensitivity (BRS), was measured with the non-invasive sequence method (Nevrokard™ BRS software, version 5.1.3, Nevrokard, Ljubljana, Slovenia). Input data for the software were generated with a Finapress monitor and the electrocardiogram. Briefly, the software identified sequences in which the electrocardiogram R–R intervals and the SBP and DBP concurrently increased or decreased for over three beats. The minimum change in blood pressure was set at 1 mm Hg and the minimum change in the R–R interval was set at 5 ms. The software used the combined results of the upward and downward sequences to calculate the BRS indices. The BRS was expressed in ms per mm Hg. This non-invasive method provided accurate assessments of BRS, comparable with those obtained with invasive methods.[15]

Biochemical indices

Plasma catecholamine concentrations were determined with high-pressure liquid chromatography and a commercial reagent kit (Chromsystems, Munich, Germany). Plasma neuropeptide Y (NPY) concentrations were estimated with the EURIA-NPY radioimmunoassay (Euro-Diagnostica, Malmo, Sweden). Measurement of endothelin was performed with a human endothelin-1 enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA). Plasma aldosterone concentration and plasma renin activity were determined with the DSL 8600 radioimmunoassay (Diagnostic Systems Laboratories, Webster, MO, USA) and DSL 25100 radioimmunoassay (Immunotech, Praha, Czech Republic), respectively.

Data analysis

Sympathetic bursts were identified by careful inspection of voltage changes in neurograms in a blinded manner. Sympathetic activity was expressed as the number of bursts per minute (burst frequency) and the number of bursts per 100 heart beats (burst incidence).

Statistical analysis

Statistical analysis was performed with *Statistica 8.0* software. Comparisons between baseline values in the treatment and placebo groups were performed with the unpaired Student's t-test. The responses to administration of simvastatin or placebo were analyzed with a repeated-measures analysis of variance, with time (before *vs.* after 8 weeks) as the 'within' factor and treatment (simvastatin *vs.* placebo) as the 'between' factor. Data are presented as mean ± s.d. Statistical significance was established at $P<0.05$.

RESULTS

At baseline, the groups did not differ in sex, age, body mass index, SBP, DBP, HR or lipid concentrations (Tables 1 and 2). MSNA and BRS values were not significantly different in the control and treatment groups (Table 2).

Effects of simvastatin on plasma lipids

In comparison with baseline, simvastatin treatment reduced the plasma levels of total cholesterol, LDL cholesterol and triglycerides (Table 2), but did not change HDL cholesterol. In the placebo group, no changes were observed compared with baseline in total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides (Table 2).

Recorded variables before and after simvastatin therapy

In comparison with baseline, simvastatin therapy reduced MSNA from 36.5 ± 5 to 27.8 ± 6 burst per min, P=0.001 (Figure 1) and HR from 77 ± 6.7 to 71 ± 5.4 beats per min, P=0.01. When MSNA was normalized for a number of heart beats, the sympathetic activity decreased from 47.8 ± 8 to 39.4 ± 8 bursts per 100 heart beats, P=0.001. Simvastatin increased BRS from 10.3 ± 4 to 17.4 ± 4 (P=0.04), but had no influence on SBP or DBP (Table 2). In the placebo group, no changes were observed compared with baseline in MSNA, BRS, SBP, DBP or HR (Table 2).

After simvastatin treatment, MSNA was inversely related to BRS (r=−0.94, $P<0.05$). In contrast, in the control group and before simvastatin treatment, no correlations were observed between MSNA and BRS (Figure 2).

In both investigated groups, the baseline values of MSNA and BRS were not different among subjects with and without concurrent angiotensin-converting enzyme inhibitor or β-blocker treatments.

Table 2 Effects of simvastatin and placebo before and after 8 weeks of treatment

	Simvastatin		*Placebo*		*Interaction group × time*
Parameter	*Baseline*	*After therapy*	*Baseline*	*After therapy*	*P-value*
SBP (mm Hg)	142 ± 11.8	136 ± 9.5	136 ± 9.5	131 ± 12.4	0.52
DBP (mm Hg)	91 ± 10.8	84 ± 9.8	86 ± 11.0	82 ± 7.5	0.49
HR (beats per min)	77 ± 6.7	71 ± 5.4*	75 ± 7.7	73 ± 8.0	0.01
TCHOL (mg dl^{-1})	249 ± 30.6	184 ± 28.3**	232 ± 22.1	230 ± 26.2	0.001
LDL (mg dl^{-1})	169 ± 32.5	117 ± 31.2**	157 ± 29.1	150 ± 35.1	0.01
HDL (mg dl^{-1})	44 ± 1.6	44 ± 9.2	43 ± 12.0	45 ± 0.4	0.57
TG (mg dl^{-1})	156 ± 52.1	108 ± 33.2*	159 ± 52.0	161 ± 42.3	0.06
MSNA (burst per min)	36.5 ± 5.4	27.8 ± 5.8***	33.0 ± 4.7	32.0 ± 4.8	0.001
MSNA (burst per 100 heart beats)	47.8 ± 8.4	39.4 ± 8.3***	44.5 ± 7.7	44.0 ± 7.3	0.001
BRS (ms per mm Hg)	10.3 ± 4.1	17.1 ± 4.3**	12.7 ± 6.0	11.0 ± 6.0	0.04

Abbreviations: ANOVA, analysis of variance; BRS, baroreceptor sensitivity; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; MSNA, muscle sympathetic nerve activity; SBP, systolic blood pressure; TCHOL, total cholesterol; TG, triglycerides.
P-values for treatment×time interaction term (ANOVA); *$P<0.001$, **$P<0.01$, ***$P<0.001$ *vs.* before treatment.

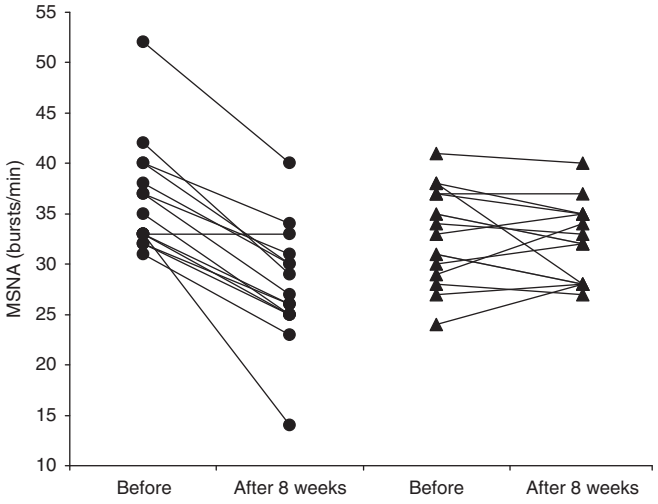

Figure 1 Muscle sympathetic nerve activity (MSNA) (burst per min) results in each participant before and at the end of therapy in (●) simvastatin and (▲) placebo groups.

Hormonal indices in simvastatin and placebo groups

At baseline, plasma levels of catecholamines, NPY, aldosterone, endothelin and renin activity were similar in both groups; none of these parameters changed significantly during treatment (Table 3).

DISCUSSION

This study showed that simvastatin reduced the sympathetic activity measured by microneurography in subjects with hypertension and hypercholesterolemia. Furthermore, we showed that treatment with simvastatin improved the baroreflex control of HR.

Effects of statins on neurohumoral activation

HMG-CoA reductase inhibitors have become one of the most commonly prescribed medication classes because of current efforts in preventing the progression of atherosclerosis and slowing its clinical sequels. Beneficial effects of statins are typically attributed to their lipid-lowering actions; however, additional cardioprotective effects have also been described, including improvement of endothelial function, upregulation of nitric oxide expression, stimulation of anti-inflammatory and antioxidant effects, and reversal of myocardial remodeling.[16–21] In addition, several studies in animal and human models found strong interactions between statins and the neurohumoral system, which could be clinically significant.[11,22–24]

Previously, convincing data suggested the involvement of enhanced sympathetic activity in the pathogenesis of cardiovascular diseases, including hypertension and hypertension-related complications.[25–27] Sympathetic overactivity might be partly explained by peripheral mechanisms, including elevated peripheral chemoreceptor activity, reduced baroreceptor sensitivity and reduced nitric oxide synthesis.[28–32] Statins can affect baroreceptor sensitivity,[33] endothelial function[17] and nitric oxide synthesis;[18] thus, the speculation arose that statins might modulate sympathetic outflow in cardiovascular disorders.[17,18,33] Accordingly, our study provided insight into the modulatory role of statins on sympathetic activation in patients with hypertension.

The modulatory role of statins on sympathetic activity

To date, only a few studies have shown that statins might decrease sympathetic activity in humans. Subjects with a wide spectrum of cardiovascular disorders have been studied. In one study with subjects who had combined hypercholesterolemia, both atorvastatin and fenofibrate partially improved the frequency and time domain indices of HR.[34] Similarly, in subjects with hypercholesterolemia, with or without coronary artery disease, prolonged atorvastatin therapy improved HRV indices, but showed no correlation between post-treatment LDL concentrations and HRV indices.[35] In a study of 80 subjects with New York Heart Association class III heart failure, atorvastatin therapy resulted in significant increases in the HRV time domain indices.[13] In that study, therapy was associated with a reduction of cholesterol; however, the atorvastatin concentration was not correlated with changes in the HRV indices. The findings in this and other studies have suggested that a reduction in sympathetic activity after statin treatment may be associated with mechanisms other than those that lower plasma lipids.

We found no differences in plasma catecholamine concentrations before and after simvastatin therapy. This was consistent with findings on subjects with heart failure treated with statins, who showed no changes in plasma noradrenaline concentrations.[36] However, another study of subjects with coronary artery disease showed that, compared

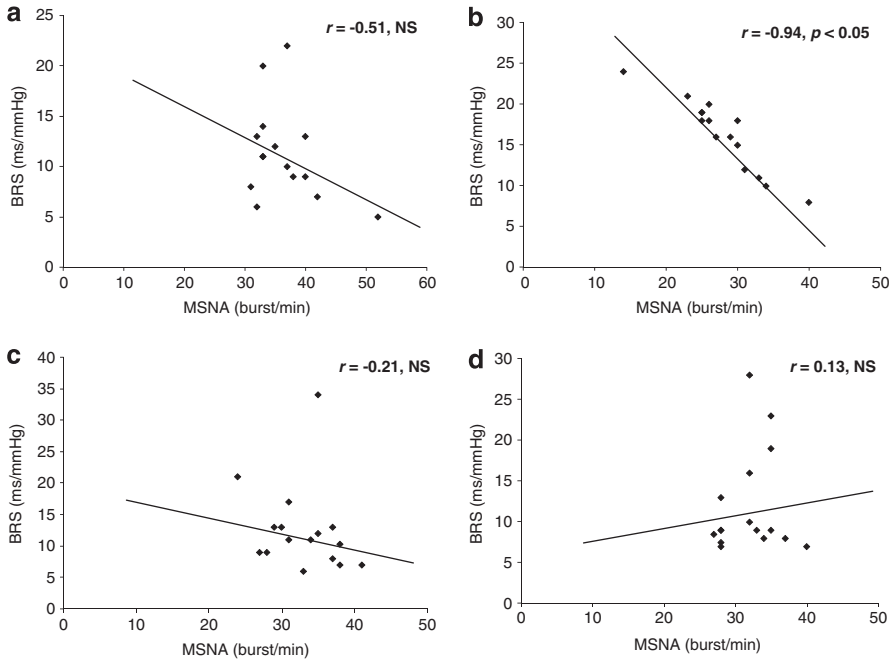

Figure 2 Correlation between baroreceptor sensitivity (BRS) (ms per mm Hg) and muscle sympathetic nerve activity (MSNA) (burst per min) in simvastatin and placebo groups before and after therapy. (**a**) Simvastatin before therapy, (**b**) simvastatin after therapy, (**c**) placebo before therapy and (**d**) placebo after therapy.

Table 3 Effects of simvastatin and placebo on hormonal indices before and after 8 weeks of treatment

	Simvastatin		*Placebo*		*Interaction group × time*
Parameter	*Baseline*	*After therapy*	*Baseline*	*After therapy*	P
Noradrenaline (pg ml^{-1})	361.0 ± 126	419.4 ± 301	354.8 ± 196	334.9 ± 109	0.50
Adrenaline (pg ml^{-1})	65.0 ± 44.1	63.0 ± 41.7	47.2 ± 24.3	46.7 ± 30.3	0.48
NPY (pg ml^{-1})	82.5 ± 17.9	76.9 ± 11.1	94.0 ± 14.1	87.8 ± 19.9	0.90
PRA (ng ml^{-1} h^{-1})	2.7 ± 2.6	2.7 ± 2.6	1.8 ± 1.1	1.6 ± 1.1	0.37
Aldosterone (pg ml^{-1})	115.2 ± 49.6	107.7 ± 42.5	119.1 ± 51.0	87.5 ± 20.5	0.09
Endothelin (μg ml^{-1})	1.38 ± 1.56	0.74 ± 0.67	0.57 ± 0.44	0.98 ± 0.94	0.07

Abbreviations: NPY, neuropeptide Y; PRA, pravastatin.

with placebo, atorvastatin reduced plasma noradrenaline measured at rest in the recumbent position.[37] The lack of changes in plasma noradrenaline in our study may have resulted from the small number of subjects included, or it may have reflected the fact that circulating noradrenaline represents only a small fraction of the neurotransmitters secreted from nerve terminals. Apart from catecholamines, NPY is a potent neurotransmitter that mediates the sympathoadrenomedullary system. Many studies have shown that NPY is a long-acting vasoconstrictor that directly modulates the effects of other mediators, including noradrenaline, serotonin and angiotensin II.[38] To date, no studies have investigated the influence of statins on plasma NPY. In our analysis, no changes in hormone concentrations were observed after lipid-lowering therapy; however, again, we may have been limited by the small number of observations.

As the reproducibility and sensitivity of most plasma catecholamine assays are low, we used microneurography recordings to study sympathetic activity. The influence of several different drugs on sympathetic activity has previously been studied with microneurography, but only a few investigations were dedicated to statins. Previously, we showed that a 40 mg dose of atorvastatin reduced sympathetic activity. However, that study was performed without a placebo control.[39] Another investigation on heart failure subjects showed that MSNA was increased after discontinuing statin therapy and was restored to basal values after resuming therapy.[36] In this study, the baseline values of sympathetic activity in hypertensive subjects were similar to those reported by other authors.[40,41] We showed that 2 months of therapy with simvastatin reduced sympathetic nervous activity.

Mechanisms underlying statin's modulatory effects on sympathetic activity

The mechanisms that underlie the beneficial effects of statins on autonomic function have not been clearly elucidated. However, several mechanisms have been suggested; for example, statin inhibition of atherosclerosis within the aortic arch and carotid arteries might improve the sensitivity of the high pressure baroreceptors.[33] As a decreased baroreflex contributes to impaired sympathovagal balance, it is possible that an improvement in BRS will lead to an inhibition of sympathetic activity. Indeed, in this study, simvastatin improved the baroreflex control of HR, and this was inversely related to the decrease

in MSNA. Furthermore, no correlation was found between the MSNA and the baroreflex control of HR in the placebo group or in either group before therapy. Therefore, we hypothesize that the improvement in BRS with simvastatin therapy may have an important role in the subsequent decrease of MSNA in subjects with hypertension and hypercholesterolemia. However, we recognize that the influence of statins on BRS may be highly variable, depending on the time of therapy, type of statin, its lipid-lowering potency and the intensity of atherosclerosis progression in different groups of patients.

Other studies have shown that the mechanisms underlying the sympathoinhibitory effects of statins may involve their inhibitory effects on the renin–angiotensin system and endothelins. In this study, no changes in plasma renin or aldosterone were detected, but endothelin concentrations tended to decrease in the treated group. It was previously established that HMG CoA reductase inhibitors can downregulate angiotensin I and endothelin receptor expression and inhibit the production of angiotensin II and endothelin.[42,43] The downregulation of angiotensin I receptors in the carotid bodies can reduce tonic chemoreflex activity.[44] Moreover, both angiotensin II and endothelin are known to stimulate sympathetic nerve traffic in the central nervous system, sympathetic ganglia and sympathetic nerve endings. In this study, some patients were taking drugs that might potentially influence sympathetic outflow, for example, angiotensin-converting enzyme inhibitors and β-blockers. Only a few studies have investigated this issue, and the results were ambiguous. In one study in patients with chronic heart failure, therapy with the angiotensin-converting enzyme inhibitor benazepril resulted in a reduction in MSNA.[45] On the other hand, in studies in subjects with hypertension, therapy with the β-blockers bisoprolol and atenolol did not influence the sympathetic drive measured with MSNA.[46,47] Furthermore, studies with regard to calcium channel blockers showed that chronic therapy did not change MSNA.[48] In our study, patients had been taking antihypertensive drugs for at least 3 months before the study. Therapy was unchanged during the study period, as reflected by BP and HR values; therefore, the changes we detected in sympathetic drive were attributed to the effects of statins.

In conclusion, this study showed that simvastatin exerted inhibitory effects on sympathetic nervous activity in subjects with hypertension and hypercholesterolemia. The potential mechanism of that action may be related to improvements in BRS; however, other mechanisms may be involved.

PERSPECTIVE

The practical implications of these data are highly relevant to the management of many cardiovascular disorders. As hypertension and hypercholesterolemia commonly coexist and contribute to the progression of atherosclerosis and increased cardiovascular risk, a pharmacotherapy that targets both disorders is strongly needed. More studies are necessary to corroborate the presented findings and explain the mechanisms underlying the sympathoinhibitory effects of statins.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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