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ORIGINAL ARTICLE

Influence of short-term simvastatin administration on parameters of autonomic nervous system activity and blood pressure in hypercholesterolemic patients with or without hypertension

Summary

Background The beneficial effects of statins are probably not exclusively related to lipid lowering activity. Therefore, we investigated the effect of simvastatin on blood pressure and heart rate variability (HRV), which can be used for studying autonomous nervous system activity.

Material and methods In a prospective, placebo-controlled, crossover trial, we studied 9 males and 11 females aged 55.2 ± 9.7 years with hypercholesterolemia (TC > 220 mg/dl), and normal blood pressure or essential hypertension stage 1–2. After 4 weeks of dietary modifications and placebo administration all subjects were given 20 mg of simvastatin for 4 weeks, followed by a placebo for another 4 weeks. Office and 24-h blood pressure (ABPM), the biochemical parameters of neuroendocrine function and HRV were evaluated. Time-domain and frequency-domain variables were studied such as: SDNN, r-MSSD, pNN50, TP, HF, LF and LF/HF ratio.

Results All subjects had significant decrease in total and LDL-cholesterol as well as triglycerides. However, four weeks of simvastatin was not associated with a significant change in office or ambulatory blood pressure. Treatment did not affect basal or stimulated plasma levels of catecholamines, aldosterone, cortisol, neuropeptide Y, renin activity. The differences in HRV between groups did not reach statistical significance. No significant correlation between changes in serum lipid levels and change in cardiac autonomic indices was found.

Conclusions This short, prospective, cross-over study has not shown significant effects of simvastatin on blood pressure, biochemical parameters of neuroendocrine function and heart rate variability (HRV) parameters in patients with hypercholesterolemia with or without hypertension.

key words: hypercholesterolemia, blood pressure, heart rate variability, HMG-CoA reductase inhibitors

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Background

In many large, controlled, clinical trials, statins — HMG-CoA reductase inhibitors, have proved to reduce cholesterol synthesis effectively and decrease the risk of cardiovascular events [1, 2]. The benefits of statin therapy cannot be fully explained on the basis of a reduction in plasma cholesterol levels and additional mechanisms have been suggested [3]. Since HMG-CoA reductase inhibitors can restore endothelial function [4], their influence on blood pressure has been analysed in several animal and human studies with conflicting results. Glorioso *et al.* [5], in a double-blind, placebo-controlled trial, described a significant decrease in both systolic and diastolic blood pressure in patients with hypertension and hypercholesterolemia treated with pravastatin. In earli-

er, open-label studies, authors [6] showed that the addition of a statin to existing anti-hypertensive treatment improved blood pressure control. Another group of researchers, found a decrease in systolic blood pressure in normotensive subjects with hypercholesterolemia treated with statin, with most of the reduction in the first month of treatment [7]. In another study, adding simvastatin to antihypertensive treatment decreased blood pressure [8]. Moreover, therapy with HMG-CoA reductase inhibitors diminished blood pressure response to mental stress [9] and norepinephrine or angiotensin II infusion [10] in patients with hypercholesterolemia and hypertension. However, in another study, there was no difference in both systolic and diastolic blood pressure in patients treated with statin added to antihypertensive therapy [11].

Therefore, we planned a placebo-controlled, crossover trial to evaluate the effect of simvastatin — a natural HMG-CoA reductase inhibitor, on blood pressure in hypertensive and normotensive subjects with hypercholesterolemia. To investigate the potential mechanisms of the effects of statin, we assessed basal and stimulated levels of various biochemical parameters reflecting neuroendocrine activity. Additionally, we used heart rate variability (HRV) to study the sympathetic and parasympathetic function of the autonomic nervous system in the patients.

The autonomic nervous system plays an important role in blood pressure regulation [11, 12]. Spectral analysis of HRV can be used to assess the impact of sympathetic and parasympathetic influences on the cardiovascular system [12, 13]. In several studies abnormalities of HRV analysis in hypertension have been found [14–17]. HRV measurements are noninvasive, have good reproducibility if used under standardised conditions [18–20]. Basically, HRV can be assessed in two ways: by calculation of indices based on statistical operations on R-R intervals (time domain analysis) [21] or by spectral (frequency domain) analysis of an array of R-R intervals [22] Analysis can be performed on 24-hour ECG recordings.

Material and methods

Subjects

We studied 9 males and 11 females aged 55.2 ± ± 9.7 years (range: 29–71) with hypercholesterolemia (fasting total plasma cholesterol level > 220 mg/ /dl), divided into 2 groups according to blood pressure level. Subjects with essential hypertension (HTN) had diastolic blood pressure > 90 mm Hg and < 110 mm Hg, and systolic blood pressure > 140 mm Hg and < 180 mm Hg. Subjects were included in the normotensive group (NT) if each reading of their blood pressure was below 140 mm Hg systolic and 90 mm Hg diastolic. Blood pressure was measured with the patient in a seated position between 8 and 10 a.m. by a physician. Four consecutive measurements were taken over a 10 minute period with a mercury sphygmomanometer, and the average of the last 3 values taken was used.

The exclusion criteria were as follows: an elevation of serum transaminases or creatine phosphokinase, a diagnosis of kidney disease, diabetes mellitus, a history of myopathies, unstable angina, congestive heart failure, any other severe condition with a poor prognosis. Women with child-bearing potential, nursing or pregnant women were excluded. None of the subjects had been treated previously with lipid--lowering drugs.

The protocol was approved by the Ethical Committee of the Medical University of Warsaw. All subjects gave their written informed consent to participate in the study.

Study protocol

A total of 20 participants meeting these criteria were enrolled into a four week run-in phase of the study. During this period they received dietary advice and were given a placebo between 7 and 9 p.m. each day. The patients had been counselled on the diet by a study physician and a diet program which paralleled the dietary recommendations of the American Heart Association (AHA) was implemented [23]. No lipid lowering and hypotensive drugs were allowed throughout the entire run-in phase. Compliance with the study protocol was assessed by a pill-count (100 × number of pills taken/number of pills prescribed) and an interview every 4 weeks. Three subjects did not complete the study due to withdrawal of consent or unsatisfactory compliance (less than 80%).

At the end of the run-in phase 17 participants (8 normotensives, 9 hypertensives) had met the inclusion criteria. Their data are presented in Table I. On the following visit (week 0) an office blood pressure, 24-h ambulatory blood pressure measurements (ABPM), and heart rate variability (HRV) measurements were performed. Daily urine was collected and fasting blood samples were drawn by venipuncture between 8 and 10 a.m., plasma was separated immediately and stored at –70°C until it was assayed. From then on, all subjects were given 20 mg of simvastatin (Zacar, provided by MSD Polska, Warsaw, Poland) between 7 and 9 p.m. every day for 4 weeks. After completion of this period of the study, simvastatin

Table I. Baseline characteristics of subjects studied

Parameters	Hypertension n = 9	Without hypertension n = 8	p value (Mann-Whitney U test)
Age (years)	56 ± 7	55 ± 8	0.73
Gender (male/female)	6M/3F	2M/6F	
SBP [mm Hg]	154.8 ± 10	125.1 ± 8	**< 0.01**
DBP [mm Hg]	97.7 ± 4	80.1 ± 4	**< 0.01**
Pulse pressure [mm Hg]	50.6 ± 7	44.6 ± 6	0.13
24-hour SBP [mm Hg]	136.7 ± 9	117.9 ± 8	**< 0.01**
24-hour DBP [mm Hg]	86 ± 5	72.2 ± 3	**< 0.01**
Total cholesterol [mg/dl]	226.7 ± 35	241 ± 28	0.52
LDL cholesterol [mg/dl]	139.6 ± 30	152.6 ± 17	0.40
HDL cholesterol [mg/dl]	46.38 ± 9.47	53 ± 10.52	0.15
Triglycerides [mg/dl]	207.6 ± 88	194.1 ± 96	0.83
Norepinephrine [ng/ml]	227.6 ± 55	247.1 ± 2	0.84
Epinephrine [ng/ml]	28.7 ± 12	20.9 ± 43	0.28

was replaced with a placebo for another 4 weeks. Subjects were investigated on each visit after the run-in phase (week 0), after 4 weeks on simvastatin (week 4) and 4 weeks of crossover treatment with a placebo (week 8). Studies included a medical history and physical examination, office and ABPM blood pressure, HRV, blood and daily urine collection. Plasma levels of epinephrine (E), norepinephrine (NE), neuropeptide Y (NPY), were measured at rest and after stimulation. Blood samples were drawn after 30 minutes of rest in the recumbent position. Then subjects were kept standing for 8 minutes and blood was collected again.

Laboratory measurements

Plasma total (TC) and HDL cholesterol, triglycerides, electrolytes, creatinine, creatine phosphokinase, creatine phosphokinase-MB, aspartate aminotransferase, alanine aminotranspherase, were measured using routine biochemical methods. LDL-cholesterol was determined by means of Friedewald formula. Plasma norepinephrine and epinephrine concentrations were determined by high performance liquid chromatography (HPLC, Bio-Rad). Norepinephrine and epinephrine in urine were measured by the fluorometric method of Anton *et al.* [24], and urinary metanephrines colorimetrically [25].

Plasma renin activity, aldosterone, cortisol and neuropeptide Y were determined by means of a radioimmunoassay (RIA).

Twenty-four hour blood pressure monitoring (ABPM) was performed with a Space Labs 90207 monitor (Redmont, Washington, USA). Readings were obtained every 15 minutes during the day (06:00 to 23:00) and every 20 minutes at night (23:00 to 06:00).

24-hour ECG recordings were performed on the Medilog Excel 2 System (Oxford Instruments Ltd., Abington, Oxon, UK) and were processed for HRV analysis. Ambulatory data were recorded on standard cassette tapes with the use of Oxford 4000 series recorders. The fast Fourier transform was then calculated.

The time-domain variables measured were as follows: the standard deviation of normal RR intervals (SDNN), the percentage of differences between adjacent normal RR intervals > 50 ms (pNN50), the square root of the mean of squared differences between adjacent normal RR intervals (r-MSSD).

The frequency domain variables included as follows: total power (TP, 0.00–0.50 Hz), high frequency power (HF, 0.15–0.40 Hz), low frequency power (LF, 0.04–0.15 Hz), and LF/HF ratio.

Statistics

The study was a prospective, cross-over without blinding for simvastatin. Data presented as a mean ± SD. The Mann-Whitney rank-sum test, and Wilcoxon signed-rank test for paired data were used in analysing the data as appropriate. The Spearman correlation was employed to study the relationship between cholesterol lowering and blood pressure levels. P values less than 0.05 were considered statistically significant.

Results

Effect of simvastatin therapy on plasma lipid concentration

All subjects who completed 4 weeks of simvastatin therapy showed a significant decrease in both total and LDL-cholesterol levels. TC was reduced by 26.7% and LDL-cholesterol by 43.9% in normotensive subjects, and by 30.1% and 38.4% in hypertensives, respectively. In both groups, triglycerides plasma levels at week 4 were lower as compared to week 0, and these differences reached the level of statistical significance in both groups of subjects. Plasma concentration of HDL-cholesterol did not change during the simvastatin treatment phase. After switching to a placebo, both total and LDL-cholesterol as well as TG levels returned to pretreatment values (tab. II).

Effect of simvastatin therapy on blood pressure

After 4 weeks of the run-in phase, subjects assigned to the HTN group had higher ABPM values as compared to normotensive subjects, which remained significantly different throughout all the study periods. In hypertensives, 4 weeks of simvastatin administration were not associated with a significant change in the parameters estimated in ABPM such as: mean 24-hour, day or night systolic and diastolic blood pressure. These values did not change when patients were switched to a placebo. Similarly, mean values for these parameters were not different in normotensive subjects during visits at weeks 0, 4 and 8. In the course of simvastatin

Table II. The effect of simvastatin treatment on blood pressure and biochemical parameters of neuroendocrine activity in subjects with hypercholesterolemia and normal blood pressure

Parameters	HL week 0	HL week 4	HL week 8	p value Wilcoxon test
SBP [mm Hg]	125.1 ± 8	120 ± 11	123.3 ± 7	0.17
DBP [mm Hg]	80.1 ± 4	78.2 ± 5	79 ± 4	0.62
Pulse pressure [mm Hg]	44.6 ± 6	41 ± 6	42.6 ± 5	0.15
24-hour SBP [mm Hg]	117.9 ± 8	113 ± 9.5	115 ± 7	0.86
24-hour DBP [mm Hg]	72.2 ± 3	72 ± 4	71.7 ± 3	0.34
Total cholesterol [mg/dl]	241 ± 28	176.6 ± 19*	225.1 ± 36	**0.01**
LDL cholesterol [mg/dl]	152.6 ± 17	94 ± 14*	137 ± 30	**0.02**
Triglycerides [mg/dl]	194.1 ± 96	139.9 ± 37*	195 ± 136	**0.04**
HDL cholesterol [mg/dl]	53 ± 10,5	54.6 ± 13.2	53 ± 13	0.17
Norepinephrine [ng/ml]				
0 min	247.1 ± 92.6	225 ± 164	271 ± 142	0.40
8 min	463.7 ± 112.4	466.6 ± 231	541 ± 300.4	0.88
Epinephrine [ng/ml]				
0 min	20,9 ± 2.5	22.2 ± 18.3	20.6 ± 15.4	1.00
8 min	43.1 ± 25	39 ± 28	33 ± 24	0.26
Neuropeptide Y [pg/ml]				
0 min	5.2 ± 1.7	5.6 ± 2.5	5.8 ± 2.6	0.67
8 min	6.0 ± 1.1	5.6 ± 1.7	6.3 ± 2.5	0.48
Metanephrines [μg/24h]	559,4 ± 229	597 ± 182	530 ± 167	0.67
Norepinephrine [μg/24h]	17.8 ± 10.6	16 ± 4.6	12.6 ± 2.4	0.78
Epinephrine [μg/24h]	3.4 ± 0.8	2.3 ± 0.9	2.4 ± 2	0.12
Aldosterone [ng/dl]	4.7 ± 2.3	4.5 ± 1.3	5.2 ± 3	0.49
Plasma renin activity [ng/ml/h]	0.9 ± 0.3	0.8 ± 0.6	0.8 ± 0.6	0.67
Fibrinogen [mg/dl]	292.5 ± 10	338.6 ± 34	320 ± 64*	**0.03**
Cortisol [μg/dl]	9.2 ± 1.8	9.5 ± 4.9	9 ± 4.4	0.78

administration, we observed a decrease in the office systolic blood pressure in 5 patients, and diastolic blood pressure in 4 subjects in the group of 8 normotensives with hypercholesterolemia. Among 9 hypertensive patients a small decrease in office systolic or diastolic blood pressure was noted in 3 and 5 patients, respectively. However, these changes were not paralleled in ABPM. Changes in the concentration of total cholesterol and LDL-cholesterol did not correlate with changes in the mean blood pressure (24-hour, day or night) calculated from ABPM in both groups studied.

Effect of simvastatin on biochemical parameters of neuroendocrine function

After run-in phase (week 0) plasma levels of epinephrine and norepinephrine and urinary excretion of native catecholamines and their major metabolite did not differ between normotensive and hypertensive subjects. With patients remaining in the upright position, stimulated plasma concentrations of epinephrine and norepinephrine were similar in hypertensive and normotensive patients. An increase in plasma catecholamines levels was not affected by simvastatin therapy. Also, no significant change in plasma levels of neuropeptide Y, aldosterone, cortisol and plasma renin activity was observed.

Effect of simvastatin therapy on heart rate variability (HRV) parameters

All HRV parameters, except of the LF/HF ratio, were lower in patients with hypertension when compared with normotensive subjects (tab. IV). However, the differences were not statistically significant. In persons with normal blood pressure, treatment with simvastatin led

Table III. The effect of simvastatin treatment on blood pressure and biochemical parameters of neuroendocrine activity in subjects with hypercholesterolemia and hypertension

Parameters	HTN week 0	HTN week 4	HTN week 8	p value Wilcoxon test
SBP [mm Hg]	154.8 ± 10	155.7 ± 12	154.6 ± 11	0.67
DBP [mm Hg]	97.7 ± 4	98.7 ± 7	96.5 ± 5	0.68
Pulse pressure [mm Hg]	50.6 ± 7	53 ± 9	51 ± 8	0.07
24-hour SBP [mm Hg]	136.7 ± 9	139.8 ± 14	136.9 ± 12	0.26
24-hour DBP [mm Hg]	86 ± 5	86.8 ± 8	85.9 ± 7	0.37
Total cholesterol [mg/dl]	226.7 ± 35	158.4 ± 33*	224.9 ± 42	**0.01**
LDL cholesterol [mg/dl]	139.6 ± 30	78.3 ± 22*	135.7 ± 40	**0.02**
Triglycerides [mg/dl]	207.6 ± 88	180 ± 93*	204.2 ± 96	0.04
HDL cholesterol [mg/dl]	46.4 ± 9.5	48.3 ± 10	47 ± 9.8	0.09
Norepinephrine [ng/ml]				
0 min	227.6 ± 55	223 ± 67	238 ± 65	0.78
8 min	445.3 ± 89	445 ± 52	507.6 ± 161	1.00
Epinephrine [ng/ml]				
0 min	28.7 ± 12	20 ± 8	19 ± 8	0.26
8 min	43.3 ± 21	36 ± 7	31 ± 19	0.48
Neuropeptide Y [pg/ml]				
0 min	8.1 ± 9	6.7 ± 8	7.1 ± 6	0.21
8 min	7.5 ± 8.2	7.1 ± 6.2	8.4 ± 7.2	0.51
Metanephrines [μg/24h]	563 ± 213	565 ± 182	514 ± 177.2	0.34
Norepinephrine [μg/24h]	21.3 ± 4.5	21.4 ± 4	13.6 ± 3.2	0.68
Epinephrine [μg/24h]	2.77 ± 1.2	2.8 ± 0.5	2.0 ± 1	0.22
Aldosterone [ng/dl]	4.4 ± 1.7	4.8 ± 1.4	4.5 ± 1.4	0.61
Plasma renin activity [ng/ml/h]	0.8 ± 0.2	0.8 ± 1.4	1.0 ± 0.4	0.68
Fibrinogen [mg/dl]	243 ± 45	269 ± 61	275 ± 20.6	0.39
Cortisol [μg/dl]	7.3 ± 3.6	8.1 ± 2.6	7.9 ± 3	0.78

Table IV. HRV parameters in subjects with hypercholesterolemia and normal blood pressure or with hypertension

Parameters	Without hypertension n = 8	Hypertension n = 9	p value (Mann-Whitney U test)
SDNN [ms]	131.9 ± 35	120.3 ± 36	0.74
r-MSSD [ms]	46.14 ± 37	24.9 ± 14	0.25
PNN50 [ms]	3.95 ± 4	1.4 ± 1	0.44
LF [ms^2]	486.9 ± 353	287.8 ± 164	0.27
HF [ms^2]	188.8 ± 215	69.4 ± 51	0.22
TP [ms^2]	1677.7 ± 992	1270.4 ± 577	0.40
LF/HF	3.66 ± 1.8	4.4 ± 1	0.25

Table V. The effect of simvastatin treatment on HRV parameters in subjects with hypercholesterolemia and normal blood pressure

Parameters	HL week 0	HL week 4	HL week 8	p value Wilcoxon test
SDNN [ms]	131.9 ± 35	120.2 ± 29	141.6 ± 54	0.28
r-MSSD [ms]	46.14 ± 37	28 ± 19	54.8 ± 50	0.14
PNN50 [ms]	3.95 ± 4	4.92 ± 6.4	7.7 ± 8	0.46
LF [ms^2]	486.9 ± 353	561 ± 499	705.3 ± 639	0.71
HF [ms^2]	188.8 ± 215	219.8 ± 309	355.4 ± 378	0.46
TP [ms^2]	1677.7 ± 992	1892.2 ± 1469	2319.3 ± 1700	0.14
LF/HF	3.66 ± 1.8	3.2 ± 1.09	2.2 ± 0.4	0.71

Table VI. The effect of simvastatin treatment on HRV parameters in subjects with hypercholesterolemia and hypertension

Parameters	HTN week 0	HTN week 4	HTN week 8	p value Wilcoxon test
SDNN [ms]	120.3 ± 36	124.2 ± 40	121.1 ± 57	0.24
r-MSSD [ms]	24.9 ± 14	42.6 ± 33	32.8 ± 25	0.13
PNN50 [ms]	1.4 ± 1	1.3 ± 1	3.02 ± 2	0.73
LF [ms^2]	287.8 ± 164	297.6 ± 124	396.8 ± 269	0.31
HF [ms^2]	69.4 ± 51	69.3 ± 32	104.7 ± 44	0.61
TP [ms^2]	1270.4 ± 577	1337.7 ± 523	1577.1 ± 1088	0.61
LF/HF	4.4 ± 1	4.63 ± 1.5	3.7 ± 1.4	0.17

to an increase in the time-domain parameter pNN50 and all frequency parameters (LF, HF, TP), except LF/HF. Hypertensive patients showed an increase in all parameters after simvastatin treatment. In both groups these changes did not reach statistical significance. Moreover, there was a further increase in most of the parameters in the following weeks with a placebo. These changes might be attributed to the relatively high variabilities in HRV parameters among the patients.

Discussion

In our small group of patients, therapy with HMG-CoA reductase inhibitor, simvastatin, did not

influence blood pressure levels. There was no effect of simvastatin on blood pressure in subjects with hypercholestorolemia, both normotensive and hypertensive. All subjects had a satisfactory response to hypolipemic therapy and during the end of the active treatment period serum levels of total and LDL cholesterol decreased significantly by 26.7% and 43.9%, respectively in normotensive patients and by 30.1% and 38.4% in those who were hypertensive. These results are similar to the reported efficacy of simvastatin, which also allows one to assume good compliance with the experimental protocol.

In a similar, placebo-controlled study, Glorioso *et. al.* [5] described decreases in systolic and diastolic blood pressures by 8 and 5 mm Hg in 25 subjects treated with pravastatin for 16 weeks. The authors noted a significant decrease in diastolic blood pressure after 4 weeks of therapy but for systolic blood pressure, the difference between the HMG-CoA reductase inhibitor and the placebo reached statistical significance after 12 weeks of therapy. However, in our study we could not detect any significant change in blood pressure after 4 weeks of administration of simvastatin as compared to pretreatment placebo. In the above-mentioned study with pravastatin, systolic blood pressure decreased in 23 subjects and diastolic pressure in 22 subjects who were among 25 patients who received pravastatin therapy compared to a pretreatment placebo. In a small open label study, Abetel *et al.* described the hypotensive effect of fluvastatin in 12 out of 23 treated patients with hypertension and hypercholesterolemia [26].

In our study, simvastatin treatment was followed by a similar period of placebo administration to investigate if any changes in blood pressure might be associated with treatment with HMG-CoA reductase inhibitors. We found a decrease in office systolic or diastolic blood pressure in some hypertensive patients and normotensive subjects during HMG-CoA therapy, but in subjects who experienced a marked lowering of blood pressure during statin administration, replacement of simvastatin with a placebo was not associated with a tendency to elevate blood pressure. These changes were not associated with similar differences in mean values of blood pressure obtained during 24-hour measurements. Thus, in our study, they may represent variations in blood pressure levels obtained during standard conditions in a clinical setting.

It is possible that extending the period of HMG-CoA administration in our study could have induced significant changes in blood pressure values. In other studies which have reported a significant hypotensive effect of statin treatment, a significant lowering of blood pressure was noted after about 4 weeks of administration of HMG-CoA reductase inhibitor and continued to decrease during treatment [8, 9]. Moreover, the number of patients included in our study could be too low to find any potential effect of the treatment on blood pressure. Glorioso *et al.* [5] were able to detect a significant reduction in blood pressure, studying a group of 25 patients. We investigated, altogether, 17 subjects and could not observe any tendency towards reduction in blood pressure while an expected lowering of blood cholesterol was noted. In our study four weeks of simvastatin therapy decreased total and LDL-cholesterol by 30.1% and 43.9% in hypertensive subjects, respectively. Glorioso *et al.* after 16 weeks of administration of pravastatin described a decrease in the total cholesterol level by 17% and LDL cholesterol by 25%. This was accompanied by a reduction of systolic and diastolic blood pressure by 8 and 5 mm Hg as compared to the baseline. Many epidemiological studies have found a positive relationship between cholesterol levels and blood pressure [27–30]. This association may be due to common risk factors (age, obesity, dietary habits) related to increases in both cholesterol and blood pressure. However, results of The Tromso Study [27] suggest that there are biological interrelations (*i.e.* similar causative factors like hyperinsulinism) between blood pressure and atherogenic blood lipid fractions. Therefore, one might expect a reduction of blood pressure due to a lowering of blood lipid levels by itself. Despite a consistent decrease in the serum concentration of cholesterol we did not observe similar changes in blood pressure. In the studies which reported a significant reduction of blood pressure during treatment with HMG-CoA reductase inhibitors, there was no association between blood pressure and serum cholesterol levels [5, 26]. Moreover, our results did not show any correlation between serum cholesterol levels (basal or degree of reduction during therapy) and blood pressure changes. These findings suggest that potential hypotensive effect of statins is not related to lipid-lowering. Possible mechanisms might include decreased NO availability [31, 32], vessel wall reactivity to pressor agents [33], changes in endothelin production [34] or an anti-proliferative effect on vascular smooth muscle cells [35].

We measured the synthesis of epinephrine, norepinephrine and their major metabolites both in basal and stimulated conditions during a postural test. The activation of an adrenergic response during the postural test resulted in doubled plasma levels of epinephrine and norepinephrine, but there were no differences in their levels during simvastatin treatment as compared to placebo period. Other authors have shown that 3 weeks of therapy with pravastatin re-

duced diastolic blood pressure response to the infusion of norepinephrine and angiotensin II [10]. In a study, which included 14 patients with mild hypertension and hypercholesterolemia, Straznicky *et al.* observed a trend of lower diastolic responses to isometric exercise, although without reaching a statistically significant difference [10]. It is interesting that in their study there was no difference in systolic and diastolic blood pressure after 3 weeks of pravastatin or a placebo. In another study, 6 weeks of lovastatin therapy modified blood pressure response to psychological stress [9] and the authors noted a significant correlation between total plasma cholesterol concentration and changes in systolic blood pressure.

A reduction in plasma aldosterone with statins reported by others [36] may have also played a role in decreasing blood pressure. In our study, plasma aldosterone and cortisol levels were not significantly correlated with blood pressure changes and were not affected by simvastatin therapy. The lack of effect of HMG-CoA reductase inhibitors on adrenal hormones has also been reported by others [37].

Animal studies on the effect of HMG-CoA reductase inhibitors on blood pressure has provided conflicting results. Some investigators have found decreased systemic blood pressure in spontaneously hypertensive rats (SHR) [33] as well as in mineralocorticoid-induced hypertension (DOCA-salt) [38]. In contrast to these studies, Roullet *et al.* [39, 40] found that inhibitors of HMG-CoA reductase increased the responses of resistance vessels to pressor substances and raised blood pressure in SHR. They also described similar phenomenon in human arterial segments isolated from subcutaneous fat tissue [41]. The authors suggest that HMG-CoA reductase inhibitors decrease the synthesis of farnesol which blocks the L-type voltage dependent calcium channel. Other studies in both animals and humans showed an activation of endothelial isoform of nitric oxide synthetase (ecNOS, NOS-3) with simultaneous improvement of vasodilatatory endothelial function. The augmentation of both basal and stimulated NO production was observed as soon as after 1 month of treatment with simvastatin, although no effect on systemic blood pressure was noted even after 3 months of administration [4]. In large, multicentre trials which included a substantial number of patients with hypertension, no effect of HMG-CoA reductase inhibitors on blood pressure was reported. However, these studies were not designed to test the influence of statin on blood pressure and hypertensive patients were treated to obtain satisfactory blood pressure control. If HMG-CoA reductase inhibitors possessed a significant ability to reduce blood pressure, the number of hypotensive medications would have had to be lower in a group assigned to a cholesterol-lowering regimen. None of such data are available from completed large trials [1, 42–44]. In small, open label study, Sposito *et al.* [8] described a reduction in blood pressure in patients with hypertension when HMG CoA reductase inhibitor was included into hypotensive regimen.

In essential hypertension, an enhanced sympathetic activity and a reduced vagal activity have been found by a heart rate variability (HRV) analysis. The altered sympathovagal balance of cardiac control results in less vagally mediated respiratory sinus arrhythmia and more baroreflex-related heart rate variability in patients with essential hypertension compared with normotensive controls. A reduced day-night oscillation in sympathetic activity is also found in these patients. Some investigators reported a negative correlation between the extent of coronary atherosclerosis and respiratory sinus arrhythmia measured by spectral analysis in patients who had coronary artery angiography. HRV can be used to quantify the effects of drugs on the autonomic nervous system. It has been used to investigate the mode of action of drugs in adults. The effects of some drugs on HRV have been studied in hypertensive patients [45]. With spectral analysis it is possible to unravel and quantitate sympathetic and parasympathetic activities of drugs and might give more information about their effects in cardiac diseases. Some agents with well-established roles in the treatment of cardiovascular diseases are able to restore the sympathetic-parasympathetic balance.

In our study there were lower baseline HRV parameters in patients with hypertension but these changes were not statistically significant. In the work of Singh *et al.* from the Framingham Heart Study, a low frequency parameter (LF) was associated with new-onset hypertension in men [46]. The researchers found a relationship between this parameter and the incidence of hypertension in men. The relationship was weaker in women and for diastolic rather than systolic blood pressure. The impact of LF on blood pressure was studied. A decrease in LF was associated with an increase in systolic and diastolic blood pressure [33]. An association of another HRV component *i.e.* HF with hypertension has also been reported [34]. Some methodological aspects may have played role in the differences between these two studies.

Furberg has suggested that certain statins may differ, particularly in their activities not associated with any lipid-lowering potential [47]. Glorioso *et al.* [5] in their study, described a marked reduction in blood pressure during treatment with pravastatin. Due to

fewer lipophilic properties related to its open lactone ring chemical structure, pravastatin reaches much higher plasma concentrations that other statins and may raise its potential to interact with endothelial cells [32]. Despite the lower ability of simvastatin to activate ecNOS in cultured endothelial cells as compared to pravastatin, both statins improve endothelial function in subjects with hypercholesterolemia [4, 32].

Conclusions

This short, prospective, cross-over study did not reveal any significant effects of simvastatin on blood pressure, biochemical parameters of neurocrine function and heart rate variability components in patients with hypercholesterolemia with or without hypertension. The role of HRV beyond the inspection of patients after myocardial infarction and diabetes remains questionable. It has been shown in some trials that a reduction in HRV is associated with an increase in the risk of mortality due to cardiovascular diseases and overall mortality. One thing is certain: long-term controlled studies with different statins are needed to establish the role of HMG-CoA reductase inhibitors as additional treatment for patients with hypertension.

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