Atorvastatin reduces sympathetic activity and increases baroreceptor reflex sensitivity in patients with hypercholesterolaemia and systemic arterial hypertension

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Abstract

Background: Increased sympathetic activity might be related to pathogenesis of hypertension as well as to end organ damage. Animal studies suggest that statins decrease sympathetic activity and increase baroreceptor reflex sensitivity (BRS).

Aim: To examine whether atorvastatin decreases muscle sympathetic nerve activity (MSNA) and BRS in hypercholesterolaemic and hypertensive patients.

Methods: Ten patients with essential hypertension and untreated hypercholesterolaemia (aged 43 ± 12 years) and eight healthy subjects (aged 37 ± 7 years) were enrolled in the study. In both groups the recordings of microneurography, ECG, blood pressure and BRS were performed twice, before and after 8 weeks during which the patients (but not controls) were treated with atorvastatin.

Results: Compared with controls, the patients had higher MSNA values (36.0 ± 6.6 vs. 29.8 ± 3.7 bursts/minute), mean BP levels (145.1 ± 10 vs. 124.1 ± 11.1 mmHg) and total cholesterol concentration (252.6 ± 22.6 vs. 179.8 ± 20.7 mg/dl) baseline values. Statin therapy resulted in a decrease of total cholesterol (252.6 ± 22.0 vs. 173.8 ± 26.2 mg/dl, $p < 0.05$) and MSNA (36.0 ± 6.6 vs. 28.6 ± 4.8 bursts/min, $p < 0.05$), whereas BRS values were increased (12.6 ± 5.6 vs. 18.1 ± 5.9 ms/mmHg, $p < 0.05$). Post-treatment BRS was inversely related to post-treatment MSNA ($r = –0.73$, $p < 0.05$). In the controls there were no changes in MSNA (29.8 ± 3.7 vs. 28.9 ± 2.9 bursts/min), BRS (11.9 ± 5.0 vs. 13.1 ± 4.8 ms/mmHg), total cholesterol, BP and heart rate between the first and the second measurement.

Conclusion: Atorvastatin reduces MSNA and increases BRS in hypertensive and hypercholesterolaemic patients. Decrease in sympathetic activity may be the result of improvement of baroreceptor function by atorvastatin.

Key words: sympathetic system, statins, hypercholesterolaemia, hypertension, baroreflex sensitivity

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Introduction

Hypercholesterolaemia remains an independent risk factor for cardiovascular morbidity and mortality [1]. Its relative contribution to cardiovascular risk has been documented and measured by many investigators [2-4]. Moreover, hypercholesterolaemia frequently coexists with borderline-to-mild hypertension, and both factors are associated with exaggerated cardiovascular stress reactivity [5, 6].

The HMG-CoA reductase inhibitors or 'statins' prevent coronary and cerebrovascular events in patients with high and even normal cholesterol levels [7]. Significant reduction of fatal and nonfatal episodes observed in studies on primary and secondary prevention showed that statins reduced cardiovascular events far beyond the expected hypolipidaemic effect [3, 7]. Among actions of statins which may be involved in the decrease of cardiovascular risk, the improvement of endothelial dysfunction, up-regulation of nitric oxide expression, reduction of matrix metalloproteinases expression or stimulation of anti-inflammatory and antioxidant effects, and the decrease of both blood pressure and sympathetic activity are listed [8-15].

Some studies in experimental animal models have investigated interactions between statins and neurohormonal systems, mainly the renin–angiotensin system and the sympathetic nervous system. It was reported that statins might inhibit hypercholesterolaemia-induced

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up-regulation of AT1 receptors and decrease angiotensin II-induced blood pressure elevation [16]. Experimental investigations showed also reduced sympathetic activity after simvastatin therapy in normolipidaemic rabbits with heart failure [13]. This effect of statins could be explained by decreased AT1 receptor expression in the rostral ventrolateral medulla, the site from which the sympathetic neurons project to the spinal cord and further to the peripheral vascular beds [14].

The modulatory effect of statins on AT1 receptors may have a beneficial influence on neurohumoral activation in systemic arterial hypertension. Systemic hypertension is associated with sympathetic overactivity as demonstrated by direct intraneural recordings and plasma catecholamine concentrations [17, 18]. This sympathetic excitation can be partly explained by increased peripheral chemoreceptor sensitivity and their tonic activation [19, 20]. One of the mechanisms of increased peripheral chemoreceptor sensitivity in cardiovascular disorders is AT1 receptor activation by angiotensin II [21]. Down-regulation of AT1 receptors by statin therapy could normalise peripheral chemosensitivity and result in decrease of sympathetic activation in patients with systemic arterial hypertension.

Moreover, it is also known that statins stimulate nitric oxide (NO) production, and because NO has sympathoinhibitory effects, that mechanism could indirectly contribute to the effects of statins on the sympathetic nervous system [22, 23].

Finally, one might also hypothesise that statin-related reduction of cholesterol concentration would improve the elastic function of arterial walls. As a consequence baroreceptor function can be modulated, as suggested in a recent study reporting improved baroreceptor reflex sensitivity (BRS) after statin therapy [24]. Therefore, we investigated the effects of atorvastatin therapy on sympathetic tone measured by muscle sympathetic nerve activity (MSNA) and baroreceptor sensitivity in hypertensive patients with increased cholesterol level.

Methods

Subjects

Ten males (aged 43 ± 12 years, BMI 28 ± 4 kg/m^2) with hypercholesterolaemia and mild to moderate essential hypertension, and 8 male healthy control subjects (aged 37 ± 7 years, BMI 27 ± 5 kg/m^2) were studied. Repeated measurement in the control group was performed to find out whether the reduction in MSNA in the experimental group after treatment was not related to reduced anxiety during the second recording. All patients in the experimental group were on antihypertensive therapy (calcium channel blockers – 4, beta-blockers – 2, inhibitors of angiotensin-converting enzyme – 4, diuretics – 2) which remained unchanged for 4 weeks before and during the entire study. None of them were receiving lipid-lowering medications. None of the investigated subjects was an active tobacco user. According to routine investigations and laboratory findings, secondary forms of hypertension and diabetes were excluded. Informed consent was obtained from all participants. The institutional review board of the Medical University approved the study protocol.

Measurements

Heart rate (HR) was recorded continuously (Power Lab Data Acquisition System, ADInstruments Inc, Colorado Springs, CO, USA). The arterial blood pressure (BP) was measured by a digital photoplethysmograph device capable of providing accurate beat-to-beat systolic and diastolic values (Finapress, Omeda 2300, Monitoring Systems, Englewood, CO, USA).

The MSNA signals were obtained with the microneurographic technique (nerve traffic analysis system, University of Iowa, Iowa City, USA) [25]. A recording electrode was placed in the peroneal nerve at the popliteal fossa, posterior to the fibular head, and a reference electrode was placed subcutaneously 2 to 3 cm from the recording electrode. The nerve signals were amplified (gain 70 000 to 160 000), band-pass filtered (700-2000 Hz), full-wave rectified, and integrated with a resistance-capacitance circuit (time constant 0.1 s). Criteria for adequate MSNA recording included: pulse synchrony; facilitation during the hypotensive phase of the Valsalva manoeuvre, and suppression during the hypertensive overshoot after release; and increase in response to breath holding [25]. Sympathetic bursts were identified by careful inspection of the neurogram voltage in a blinded fashion. The number of bursts per minute (burst frequency) and the number of bursts per 100 heart beats (burst incidence) were used to express sympathetic activity. Original recordings of MSNA, HR and BP are presented in Figure 1.

Baroreflex sensitivity was measured using sequence non-invasive method (Nevrokard™ BRS software, version 5.1.3, Nervokard, Ljubljana, Slovenia). Input data for the software were generated by a Finapres monitor and ECG. The software is capable of identifying sequences in which RR intervals and systolic and diastolic BP concurrently increased or decreased for over 3 beats. The minimum change in BP was set as 1 mmHg and change in RR interval as 5 ms. The software calculated the BRS index for up and down sequences. The combined results of up and down sequences were used and expressed in ms/mmHg. While 24 h intra-arterial blood pressure measurement was used for BRS calculation, also short periods (10-15 min) for the sequence method were highly reproducible [26, 27]. Therefore, 15 min of BP and HR recording was used in the study.

Study design

All recordings were performed in a calm investigation room after 30 min of supine rest. The patients and

the controls underwent the recording of MSNA, HR and continuous, non-invasive BP during 15 min before introduction of treatment in the patients. Blood samples for routine chemistry were taken after the recordings. Afterwards, 20 mg of atorvastatin (Atoris, KRKA, Nowe Mesto, Slovenia) daily was administered in the patients, while the control subjects did not receive any medication. After 8 weeks, the recording of MSNA, HR and continuous non-invasive BP was repeated followed by blood sampling in the patients and the controls.

All patients and controls were asked to stop drinking alcohol and coffee the day before the study.

Statistical analysis

Statistical analysis was performed using Statistica 5.1. Results are presented as mean ± SD. The comparison between baseline values in the controls and the patients was performed by unpaired Student's t test. The comparison of variables within the control and patient groups was done by paired Student's t test. Linear regression analysis was performed to examine the relationship between MSNA and BRS values. Statistical significance was set at $p < 0.05$.

Results

Comparison of variables between patients and controls before therapy with atorvastatin

Compared to controls, patients had higher systolic and diastolic BP, total cholesterol, LDL cholesterol and triglyceride concentrations ($p < 0.05$). No difference in HDL concentration was observed between the patients and the controls (Table I).

Patients, in comparison with controls, presented higher MSNA expressed as bursts/min and bursts/100 heart beats ($p < 0.05$) (Table II, Figure 2). Values of $BRS_{\text{up \& down sequences}}$ did not differ between patients and controls (Table II, Figure 3).

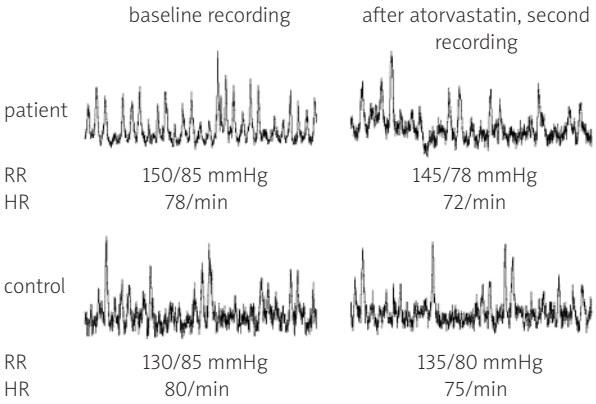

Figure 1. Original recordings of MSNA, HR, BP before and after treatment with atorvastatin in a patient and in a control subject before and after 8 weeks

Effects of therapy with atorvastatin on plasma lipid concentration

In patients, 8 weeks of atorvastatin administration decreased plasma level of total cholesterol, LDL cholesterol and triglycerides and increased plasma concentration of HDL cholesterol ($p < 0.05$). In controls, measurements taken during inclusion in the study and 8 weeks afterwards revealed similar concentration of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (Table I).

Comparison of recorded variables between patients and controls before and after therapy with atorvastatin

In patients, treatment with atorvastatin decreased MSNA expressed as bursts/min and expressed per 100 heart beats ($p < 0.05$) (Figures 1 and 2), increased $BRS_{\text{up \& down sequences}}$ ($p < 0.05$) (Figure 3) and had no effect on HR and systolic or diastolic BP during the study (Tables I and II).

Table I. Comparison of BMI, blood pressure and lipid values before and after 8 weeks of atorvastatin administration in patients and in control individuals

	Patients		Controls	
	before	after	before	after
Age	43.2 ± 12.5	–	37.1 ± 7.0	–
BMI [kg/m^2]	28.2 ± 4.2	28.7 ± 4.5	27.5 ± 5.0	28.2 ± 5.0
Systolic blood pressure [mmHg]	145.1 ± 10.3	143.2 ± 12.4	124.1 ± 11.1*	130.2 ± 10.8
Diastolic blood pressure [mmHg]	89.3 ± 10.6	84.6 ± 11.7	78.1 ± 8.9*	75.5 ± 9.2
Heart rate [beats/min]	76.1 ± 6.4	73.2 ± 6.7	71.6 ± 8.7	72.2 ± 7.6
Total cholesterol [mg/dl]	252.6 ± 22.6	173.8 ± 26.2#	179.8 ± 20.7*	178.5 ± 18.5
LDL cholesterol [mg/dl]	160.8 ± 21.0	94.6 ± 25.7#	105.1± 26.5*	98.2 ± 26.2
HDL cholesterol [mg/dl]	46.5 ± 11.2	53.2 ± 13.4#	49.0 ± 9.2	50.7 ± 10.3

**p < 0.05 compared with patients at baseline, #p < 0.05 compared with patients before treatment*

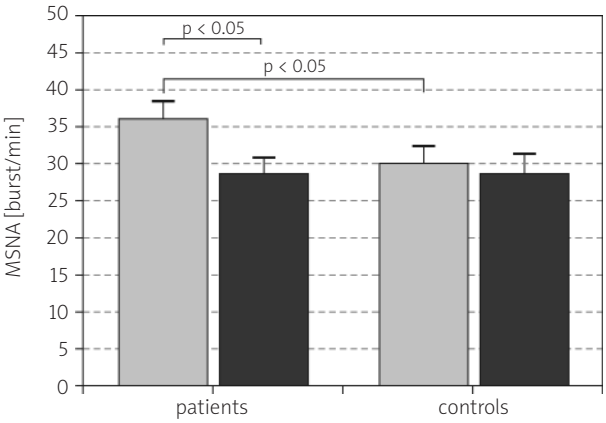

Figure 2. MSNA values before and after treatment with atorvastatin in patients and controls. Before (grey bars) and after 8 weeks (black bars)

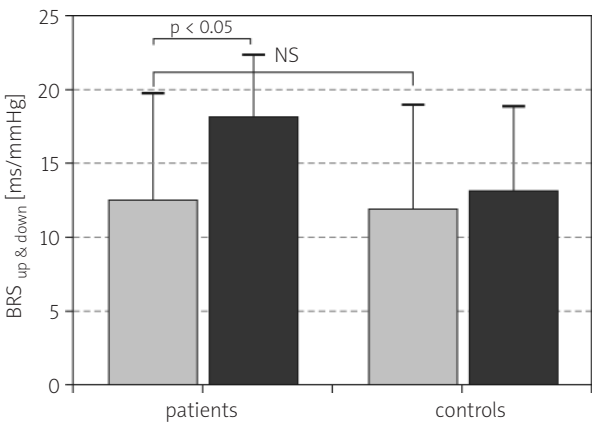

Figure 3. BRS values before and after treatment with atorvastatin in patients and controls. Before (grey bars) and after 8 weeks (black bars)

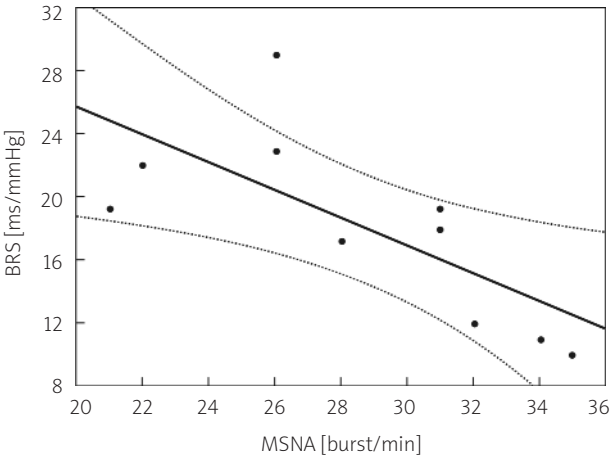

Figure 4. Linear regression analysis between MSNA (bursts/min) and BRS (ms/mmHg) values assessed after treatment with atorvastatin

In patients, in comparison with controls, atorvastatin treatment produced a decrease of MSNA expressed as bursts/min (Figures 1 and 2, Table II) and per 100 heart beats (Table II) ($p < 0.05$) and an increase in BRS ($p < 0.05$) (Figure 3, Table II). In patients, BRS after treatment was inversely related to MSNA ($r = –0.73$, $p < 0.05$) (Figure 4), while no such a relationship was observed before statin administration. No relationship between MSNA and BRS was found in the controls.

Discussion

In our study we have shown that atorvastatin produced a significant reduction of MSNA in hypertensive patients with mild hyperlipidaemia. This result was not unexpected because an influence of statins on sympathetic tone has already been shown in both experimental and clinical studies. For instance, Kishi et al. observed a significant reduction of 24 h urinary norepinephrine excretion in stroke-prone spontaneously hypertensive rats (SHR) after 30 days of therapy with atorvastatin [28]. No changes in urinary norepinephrine excretion during atorvastatin therapy were found in comparable Wistar-Kyoto rats. Diminished sympathetic activity was accompanied by a distinct reduction of BP in SHR animals. Other experiments revealed that atorvastatin might beneficially affect autonomic tone in rabbits with pacing-induced heart failure as seen by the reversal of depressed heart rate variability (HRV) and total power derived from power spectral analysis of the frequency domain [29, 30]. Another study showed a significant reduction of sympathetic outflow measured first time by direct recordings of efferent

Table II. Comparison of MSNA and BRS values before and after 8 weeks of atorvastatin administration in patients and in control individuals

	Patients		Controls	
	before	after	before	after
MSNA [bursts/min]	36.0 ± 6.6	28.6 ± 4.8#	29.8 ± 3.7 *	28.9 ± 2.9
MSNA [bursts/100 heart beats]	46.5 ± 6.2	38.4 ± 5.5#	42.3 ± 6.3 *	45.5 ± 6.6
BRS up & down sequences [ms/mmHg]	12.6 ± 5.6	18.1 ± 5.9#	11.9 ± 5.0	13.2 ± 4.8

**p < 0.05 compared with patients at baseline, #p < 0.05 compared with patients before treatment*

renal sympathetic nerve activity (RSNA) and plasma norepinephrine after simvastatin therapy in rabbits with heart failure [31].

A few other studies have investigated effects of statins on sympathetic activity in humans. Sympathetic activity in these studies was assessed by catecholamine measurements and HRV; however, no study has investigated intraneural recordings, as measured by microneurography. Statins were shown to improve frequency domain but not time domain indices of HRV after 12 weeks' therapy with atorvastatin in patients with heart failure [32]. It has been also reported that atorvastatin was effective in increasing the HRV parameters both in patients with coronary artery disease and those with congestive heart failure [33, 34]. Some authors suggest that statin class differential effects on autonomic balance may exist. Gentlesk et al. did not observe baseline HRV changes during therapy with simvastatin 20 mg daily; however, a relationship was present between LDL cholesterol reduction and sympathetic responsiveness to stress [35]. In addition, a direct comparison between pravastatin and simvastatin showed that only the former drug increased parasympathetic modulation in the hyperlipidaemic population [36]. The explanation of that finding remained unclear, however a correlation between autonomic changes and expression of Ga_{i2}, a molecular component of the parasympathetic signalling pathway, was observed in the pravastatin-treated group.

Our study showed a significant effect of atorvastatin on MSNA; however, it was accompanied by substantial plasma cholesterol reduction. Therefore, we cannot speculate whether mechanisms primarily involved in sympathetic modulation were lipid-related or not.

Several explanations have been proposed to clarify salutary neural effects of statins. First, statins may exert a modulatory effect on NO levels by both up-regulation of vascular NO synthase expression and enhancement of NO synthase activity [37, 38]. In addition, statins may increase vascular synthesis of NO by lessening isoprenylation of Rho-kinase [39]. On the other hand, it is known that enhanced NO synthesis modulates neurotransmitter function and inhibits sympathetic neural outflow in areas related to integration of sympathetic nerve activity [14].

Second, sympathoinhibitory mechanisms of statins include inhibitory effects on the renin-angiotensin system and endothelins. It was found that statins might down-regulate AT1 and ET receptors and inhibit production of angiotensin II and endothelin [40, 41]. Both angiotensin II, the main effector of the renin-angiotensin system, and endothelin-1 are known to stimulate sympathetic nerve traffic via their receptors in numerous organs, such as the central nervous system, sympathetic ganglia and sympathetic nerve endings [17, 42]. Moreover, AT1 receptors are implicated in increased peripheral chemosensitivity, and by the down-regulation of AT1 receptors in carotid bodies statins could provoke a decrease of tonic chemoreflex activation [21].

Finally, at least in a few experimental and clinical studies, statins have been found to normalise BRS, improving the integrity of the autonomic nervous system [14, 24, 29]. The results of our study show that there is a negative correlation between MSNA and BRS after treatment with atorvastatin. This finding shows that the reduction of MSNA during atorvastatin treatment may result from BRS improvement. Furthermore, we did not find any correlation between MSNA and BRS in the controls who did not receive atorvastatin and in the patients before the treatment. This observation may support a beneficial influence of atorvastatin on baroreceptor function.

In the current study, MSNA values in the patients were higher than in the controls. This result is consistent with previous studies in which patients with hypertension had higher sympathetic activity than normotensive individuals [28, 29]. There are, however, some observations that do not support the above findings [20, 43]. Discrepancies may be related to the age of investigated patients.

Several studies indicate that statins are able to reduce BP significantly, both in animals and in humans [15, 29, 44]. We did not observe hypotensive effects of atorvastatin. However, the number of our subjects was small and the duration of study limited; therefore we cannot exclude that atorvastatin would have a long-term BP lowering effect.

Some limitations should also be underlined. Our study was not placebo-controlled and we enrolled a limited number of subjects. Our patients were treated with different hypotensive agents and we cannot exclude possible influences of hypotensive therapy on the investigated variables. However, this effect would affect our results in a minor way because the doses and type of therapy were unchanged throughout the study. In addition, such external factors as level of physical activity, alcohol use and salt intake were not monitored during the whole study.

In conclusion, the present study provides data showing a modulatory effect of statin therapy on sympathetic activity in patients with hypertension and hypercholesterolaemia which may be related to the improvement of baroreflex function. Because hypertension and hypercholesterolaemia commonly coexist and are associated with increased cardiovascular risk a rationale for pharmacotherapy of both disorders is strongly needed. More studies, including placebo control groups, are necessary to corroborate our findings.

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Atorwastatyna zmniejsza aktywność współczulną i poprawia czułość odruchu z baroreceptorów u osób z hipercholesterolemią i nadciśnieniem tętniczym

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Streszczenie

Wstęp: Zwiększona aktywność układu współczulnego odgrywa istotną rolę w patogenezie nadciśnienia tętniczego i jego powikłań. Badania na modelu zwierzęcym sugerują, że statyny mogą obniżać aktywność współczulną i zwiększać czułość odruchu z baroreceptorów (ang. *baroreceptor reflex sensitivity*, BRS).

Cel: Ocena, czy atorwastatyna obniża aktywność współczulną rejestrowaną jako aktywność domięśniowych nerwów współczulnych (ang. *muscle sympathetic nerve activity*, MSNA) metodą mikroneurografii oraz jak wpływa na BRS u osób z nadciśnieniem tętniczym i hipercholesterolemią.

Metody: Zbadano 10 mężczyzn chorych na nadciśnienie tętnicze pierwotne z nieleczoną hipercholesterolemią (wiek 43 ± 12 lat) i 8 mężczyzn zdrowych (37 ± 7 lat). W obu grupach na początku i po 8 tygodniach wykonano badanie MSNA, ocenę BRS, EKG i pomiary ciśnienia tętniczego. W 8-tygodniowym okresie między badaniami statynę podawano tylko w grupie z hipercholesterolemią.

Wyniki: U chorych w porównaniu z grupą kontrolną stwierdzano wyższą aktywność współczulną podczas oceny MSNA (36,0 ± 6,6 *vs* 29,8 ± 3,7 pobudzeń/min), wyższe średnie ciśnienie tętnicze (145,1 ± 10 *vs* 124,1 ± 11,1 mmHg) i stężenie cholesterolu całkowitego (252,6 ± 22,6 *vs* 179,8 ± 20,7 mg/dl). Podawanie atorwastatyny spowodowało obniżenie stężenia cholesterolu (252,6 ± 22,0 *vs* 173,8 ± 26,2 mg/dl, $p < 0,05$) i aktywności współczulnej podczas badania MSNA (36,0 ± 6,6 *vs* 28,6 ± 4,8 pobudzeń/min, $p < 0,05$) oraz zwiększenie BRS (12,6 ± 5,6 *vs* 18,1 ± 5,9 ms/mmHg, $p < 0,05$). U chorych leczonych atorwastatyną odruch z baroreceptorów korelował ujemnie z aktywnością współczulną mierzoną podczas MSNA ($r = –0,73$, $p < 0,05$). W grupie kontrolnej między pierwszym a drugim badaniem nie stwierdzono zmian w aktywności współczulnej podczas oceny MSNA (29,8 ± 3,7 *vs* 28,9 ± 2,9 pobudzeń/min), w BRS (11,9 ± 5,0 *vs* 13,1 ± 4,8 ms/mmHg), stężeniu cholesterolu, ciśnieniu tętniczym i częstotliwości pracy serca.

Wnioski: Podanie atorwastatyny zmniejsza aktywność współczulną mierzoną MSNA i zwiększa BRS u osób z nadciśnieniem tętniczym i hipercholesterolemią. Zmniejszenie aktywności współczulnej może wynikać z poprawy BRS.

Słowa kluczowe: układ współczulny, statyny, hipercholesterolemia, nadciśnienie tętnicze, czułość odruchu z baroreceptorów

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