

Influence of the statin therapy on cardiovascular remodeling in arterial hypertension, combined with subclinical hypothyroidism

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

There is a proven relation between hypothyroidism and appearance of the pronounced structural and functional changes of the heart and blood vessels as well as atherosclerosis and its related diseases progress. At the same time, there is a lack of information regarding the influence of statins on indices of the structure and function of the heart and blood vessels in patients with arterial hypertension (AH) combined with subclinical hypothyroidism (SH).

Aim. To study the effect of the long-term statin therapy on the cardiac structure and function, as well as on vascular remodeling in patients with arterial hypertension combined with subclinical hypothyroidism.

Material and methods. The study involved 31 patients with arterial hypertension grade 1–3, stage II, of high and very high additional cardiovascular risk, with a concomitant SH. All patients received a combination of two or three first-line antihypertensive drugs at average therapeutic daily doses and atorvastatin at a dose of 20–30 mg per day. Prior to treatment and after one year of follow-up, all patients underwent an echocardiographic examination and a carotid artery scan on My Lab Seven (Italy) device as well as a 24h-blood pressure monitoring on a bifunctional device “Cardiotechnics-04” (Inkart, St. Petersburg, RF) with the simultaneous registration of BP and ECG.

Results. Under the influence of therapy, the target level of systolic blood pressure was reached in 74 % (23/31) of patients during the daytime observation period, in 65 % (20/31) of patients during the nighttime observation period; target diastolic blood pressure for the daytime observation period – in 87 % (27/31) of patients, for the nighttime observation period – in 71 % (22/31) patients. However, there was no significant change in the size of cavities of the left atrium and both ventricles, ejection fraction (before treatment 68.84 ± 5.43 %, after 67.13 ± 5.45 %), thickness of the interventricular septum and posterior wall, relative wall thickness (before treatment 0.41 ± 0.07 , after 0.41 ± 0.07 , $P = 0.871$), LV mass index (before treatment 122.29 ± 37.36 g/m², after 118.00 ± 31.00 g/m², $P = 0.849$), indices of diastolic function of the left ventricle (LV). The specific gravity of patients with eccentric LV hypertrophy after a year of treatment increased from 32 % to 39 % ($P = 0.5668$), with concentric hypertrophy decreased from 42 % to 39 % ($P = 0.8107$), with normal LV geometry – from 19 % to 16 % ($P = 0.7570$). The number of patients with AH with a concomitant SH with signs of a concentric LV remodeling remained unchanged – before treatment 6 %, after 6 %. The influence of the statin therapy on vascular remodeling in patients with AH with a concomitant SH was characterized by a tendency towards a decrease in the thickness of the intima-media complex of the right (0.769 ± 0.276 mm vs. 0.701 ± 0.222 mm, $P = 0.512$) and left (0.759 ± 0.185 mm vs. 0.745 ± 0.179 mm, $P = 0.988$) common carotid arteries.

Conclusion. In patients with AH with a concomitant SH, the antihypertensive therapy during the year with the first-line drugs with addition of statins was associated with achievement of the target SBP level in the active period in 74 %, in the passive period – in 65 % of patients (according to the 24h-BPM data), but was not accompanied by a significant decrease in the cavity size, wall thicknesses, LV mass, improvement of LV diastolic filling, reduction in thickness of the intima-media complex.

Key words:

arterial hypertension, subclinical hypothyroidism, cardiovascular remodeling, statins.

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Вплив статинотерапії на серцево-судинне ремоделювання при артеріальній гіпертензії, що поєднана з субклінічним гіпотиреозом

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Доведено зв'язок гіпотиреозу з появою виражених структурно-функціональних змін серця та судин, прогресуванням атеросклерозу та хвороб, що з ним пов'язані. Однак бракує інформації щодо впливу статинів на показники структури та функції серця та судин у хворих на гіпертонічну хворобу (ГХ), що поєднана з субклінічним гіпотиреозом (СГ).

Мета роботи – вивчити вплив тривалої статинотерапії на показники структури та функції серця та судинне ремоделювання у хворих на гіпертонічну хворобу, що поєднана з субклінічним гіпотиреозом.

Матеріали та методи. У дослідження залучили 31 особу, яка хвора на ГХ 1–3 ступеня, II стадії, високого та дуже високого додаткового кардіоваскулярного ризику з супутнім СГ. Усі пацієнти отримували комбінацію 2–3 антигіпертензивних препаратів першої лінії в середніх терапевтичних добових дозах та аторвастатин у дозі 20–30 мг на добу. До початку лікування та через рік спостереження всім хворим виконали ехокардіографічне дослідження та сканування сонних артерій на пристрої My Lab Seven (Італія) та добуве моніторингу артеріального тиску на біфункціональному пристрої «Кардіотехніка-04» («Інкарт», СПб, РФ) з одночасною реєстрацією артеріального тиску й електрокардіограми.

Результати. Під впливом терапії цільового рівня систолічного артеріального тиску за денний період спостереження досягли 74 % (23/31) хворих, за нічний період спостереження – 65 % (20/31); цільового рівня діастолічного артеріального

Ключові слова:

гіпертонічна хвороба, субклінічний гіпотиреоз, серцево-судинне ремоделювання, статини.

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тиску за денний період спостереження – 87 % (27/31) пацієнтів, за нічний період спостереження – 71 % (22/31). Але не зареєстрували вірогідну зміну розмірів порожнин лівого передсердя та обох шлуночків, фракції викиду (до лікування – $68,84 \pm 5,43$ %, після – $67,13 \pm 5,45$ %), товщини міжшлуночкової перетинки та задньої стінки, відносною товщини стінки (до лікування – $0,41 \pm 0,07$, після $0,41 \pm 0,07$, $p = 0,871$), індексу маси міокарда (до лікування – $122,29 \pm 37,36$ г/м², після – $118,00 \pm 31,00$ г/м², $p = 0,849$), показників діастолічної функції лівого шлуночка (ЛШ). Питома вага хворих з ексцентричною гіпертрофією ЛШ через рік лікування збільшилася з 32 % до 39 % ($p = 0,5668$), із концентричною гіпертрофією зменшилася з 42 % до 39 % ($p = 0,8107$), із нормальною геометрією ЛШ – з 19 % до 16 % ($p = 0,7570$). Кількість хворих на ГХ із супутнім СГ з ознаками концентричного ремоделювання ЛШ залишилась незмінною: до лікування – 6 %, після – 6 %. Вплив статинотерапії на судинне ремоделювання у хворих на ГХ із СГ характеризувався тенденцією до зменшення товщини інтима-медіального комплексу правої ($0,769 \pm 0,276$ мм проти $0,701 \pm 0,222$ мм, $p = 0,512$) та лівої ($0,759 \pm 0,185$ мм проти $0,745 \pm 0,179$ мм, $p = 0,978$) загальних сонних артерій.

Висновки. У хворих на ГХ із супутнім СГ антигіпертензивна терапія протягом року препаратами першої лінії з додаванням статинів асоціюється з досягненням цільового рівня САТ в активний період доби у 74 %, в пасивний період – у 65 % пацієнтів (за даними ДМАТ), але не супроводжувалася вірогідним зменшенням порожнин, товщини стінок, маси міокарда ЛШ, поліпшенням його діастолічного наповнення, зменшенням товщини інтима-медіального комплексу.

Ключевые слова:

гипертоническая болезнь, субклинический гипотиреоз, сердечно-сосудистое ремоделирование, статины.

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Влияние статинотерапии на сердечно-сосудистое ремоделирование при артериальной гипертензии, сочетанной с субклиническим гипотиреозом

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Доказана связь гипотиреоза с появлением выраженных структурно-функциональных изменений сердца и сосудов, прогрессированием атеросклероза и связанных с ним болезней. В то же время, недостаточно информации о влиянии статинов на показатели структуры и функции сердца и сосудов у больных гипертонической болезнью (ГБ), сочетанной с субклиническим гипотиреозом (СГ).

Цель работы – изучить влияние длительной статинотерапии на показатели структуры и функции сердца и сосудистое ремоделирование у больных гипертонической болезнью, сочетанной с субклиническим гипотиреозом.

Материалы и методы. В исследование включены 31 больной ГБ 1–3 степени, II стадии, высокого и очень высокого дополнительного кардиоваскулярного риска с сопутствующим СГ. Все пациенты получали комбинацию 2–3 антигипертензивных препаратов первой линии в средних терапевтических суточных дозах и аторвастатин в дозе 20–30 мг в сутки. До начала лечения и через год наблюдения всем больным выполнено эхокардиографическое исследование и сканирование сонных артерий на устройстве My Lab Seven (Италия) и суточное мониторирование артериального давления на бифункциональном приборе «Кардиотехника-04» («Инкарт», СПб, РФ) с одновременной регистрацией артериального давления и электрокардиограммы.

Результаты. Под влиянием терапии целевого уровня систолического артериального давления в дневной период наблюдения достигли 74 % (23/31) больных, за ночной период наблюдения – 65 % (20/31); целевого уровня диастолического артериального давления в дневной период наблюдения – 87 % (27/31) пациентов, за ночной период наблюдения – 71 % (22/31). Однако не зарегистрировали достоверное изменение размеров полостей левого предсердия и обоих желудочков, фракции выброса (до лечения – $68,84 \pm 5,43$ %, после – $67,13 \pm 5,45$ %), толщины межжелудочковой перегородки и задней стенки, относительной толщины стенки (до лечения – $0,41 \pm 0,07$, после – $0,41 \pm 0,07$, $p = 0,871$), индекса массы миокарда (до лечения – $122,29 \pm 37,36$ г/м², после – $118,00 \pm 31,00$ г/м², $p = 0,849$), показателей диастолической функции левого желудочка (ЛЖ). Удельный вес больных с эксцентричной гипертрофией ЛЖ через год лечения увеличился с 32 % до 39 % ($p = 0,5668$), с концентрической гипертрофией уменьшился с 42 % до 39 % ($p = 0,8107$), с нормальной геометрией ЛЖ – с 19 % до 16 % ($p = 0,7570$). Количество больных ГБ с сопутствующим СГ с признаками концентрического ремоделювания ЛЖ осталось неизменным: до лечения – 6 %, после – 6 %. Влияние статинотерапии на сосудистое ремоделирование у больных ГБ с СГ характеризовалось тенденцией к уменьшению толщины интима-медіального комплекса правой ($0,769 \pm 0,276$ мм против $0,701 \pm 0,222$ мм, $p = 0,512$) и левой ($0,759 \pm 0,185$ мм против $0,745 \pm 0,179$ мм, $p = 0,978$) общих сонных артерий.

Выводы. У больных ГБ с сопутствующим СГ антигіпертензивна терапія в течение года препаратами первой линии с добавлением статинов ассоциируется с достижением целевого уровня САД в активный период суток у 74 %, в пассивный период – у 65 % пациентов (по данным СМАД), однако не сопровождалась достоверным уменьшением полостей, толщины стенок, массы миокарда ЛЖ, улучшением его диастолического наполнения, уменьшением толщины интима-медіального комплекса.

Arterial hypertension (AH) is one of the most common chronic diseases. Its combination with other basic cardiovascular risk factors (age, high pulse pressure in elderly, smoking, dyslipidemia, increased levels of fasting glucose and impaired glucose tolerance, abdominal obesity and cardiovascular diseases in family anamnesis) significantly increases risks of fatal and non-fatal cardiovascular events [1]. Among additional unfavorable factors, hypothyroidism syndrome with its subclinical forms in particular

deserves special attention. Subclinical hypothyroidism (SH) is the most common condition in thyroid pathology, which in the vast majority of cases is associated with autoimmune thyroiditis [2–7]. There is a proven connection between the manifest hypothyroidism and appearance of the pronounced changes in the structure and function of the heart, as well as with the progression of atherosclerosis and diseases related to it [8]. With the development of modern diagnostic methods, more and more data are

accumulating regarding the negative effect of subclinical hypothyroidism on the cardiovascular system [9–19], albeit it is less pronounced than in other factors of cardiovascular risk [20–32].

Positive effect of the replacement therapy in various forms of the hypothyroidism has been proved, subclinical in particular. At the same time, there is a lack of information regarding the influence of statins on the indices of the structure and function of the heart and blood vessels due to their pleiotropic effects in patients with arterial hypertension combined with SH. The widespread use of statins in patients with arterial hypertension and various comorbid conditions dictates the necessity of the study of their effects in patients with AH combined with SH, and the study direction is, certainly, an issue of the current interest in modern internal medicine.

Aim

To study the effect of a long-term statin therapy on the cardiac structure and function, as well as on vascular remodeling in patients with arterial hypertension combined with subclinical hypothyroidism.

Material and methods

The studies were conducted at the clinical base of the Department of Propedeutics of Internal Medicine, Radiation Diagnostics and Radiation Therapy of ZSMU in the cardiology department of the CNI “City Hospital No. 6” of the Zaporizhzhia City Council.

After signing an informed consent, 31 patients (mean age 58 ± 10 years, 90 % women) with AH grade 1–3, stage II, of high and very high additional cardiovascular risks with the concomitant subclinical hypothyroidism were enrolled in the study. The diagnosis of AH was established in accordance with the recommendations of the Association of Cardiologists of Ukraine [1], and the diagnosis of subclinical hypothyroidism in accordance with the recommendations of the European Thyroid Association [33].

All patients received a combination of two or three first-line antihypertensive drugs at average therapeutic daily doses, and atorvastatin at a dose of 20–30 mg per day. Prior to treatment and after more than a year of follow-up, all patients underwent an echocardiographic examination and a carotid artery scan using My Lab Seven (Italy) device to study changes in the structural, geometric, and functional parameters of the heart and blood vessels. 24h-monitoring of blood pressure was performed before the initiation of therapy as well as a year later on a bifunctional device “Cardiotechnics-04” (“Incart”, St. Petersburg, RF) with the simultaneous registration of blood pressure and ECG.

Statistical processing of the material was carried out using the software package Statistica 13.0 (StatSoft, USA), license number JPZ8041382130ARCN10-J. The normality of distribution of the quantitative signs was analyzed using the Shapiro–Wilk test. Parameters that had normal distribution are presented in the form of arithmetic mean and standard deviation ($M \pm SD$).

For the indices that had a distribution that was different from normal, descriptive statistics data were provided in the form of median and lower and upper quartile –

Me (Q25; Q75). Comparisons of the quantitative indices across the groups were carried out using the Student’s and Mann–Whitney criteria, depending on the character of distribution. Qualitative indices were compared using Pearson’s χ^2 . A difference of $P < 0.05$ was considered statistically significant. All tests were two-sided.

Results

Under the influence of antihypertensive therapy with addition of atorvastatin, 74 % (23/31) of patients reached the target level of the systolic blood pressure during the daytime observation period, 65 % (20/31) of patients – during the nighttime observation period; target diastolic blood pressure for the daytime observation period was reached in 87 % (27/31) of patients, while for the nighttime observation period – in 71 % (22/31) of patients.

However, under the influence of therapy, there was no significant change in the size of the cavities of the left atrium and both ventricles. The size of the left atrium before the treatment was 4.13 ± 0.48 cm, after 4.30 ± 0.78 cm ($P = 0.617$). The end-diastolic size of the left ventricle before treatment was 5.10 ± 0.60 cm, after a year of therapy 5.04 ± 0.57 cm, ($P = 0.751$). The end-systolic size of the left ventricle before treatment was 3.11 ± 0.38 cm, and after 3.06 ± 0.45 cm ($P = 0.720$). The diastolic size of the right ventricle before the treatment was 1.85 ± 0.60 cm, after a year of follow-up 2.01 ± 0.47 cm, the changes were statistically insignificant ($P = 0.281$).

The absence of changes in the end diastolic and systolic sizes of the left ventricular cavity, as expected, didn’t lead to statistically significant ($P = 0.262$) changes in its ejection fraction at the end of the annual follow-up period (before treatment 68.84 ± 5.43 %, after 67.13 ± 5.45 %).

No significant changes in thicknesses of the interventricular septum and the posterior wall of the left ventricle were observed. Before the beginning of treatment IVSd was 1.00 ± 0.19 cm, after it became 1.04 ± 0.20 cm, the difference is insignificant ($P = 0.460$). LVPWd before the treatment was 1.04 ± 0.19 cm, after 1.02 ± 0.70 cm, the difference is also insignificant ($P = 0.632$).

Due to the absence of the significant changes in the sizes of the left ventricular cavity and its walls, there were no significant changes in the relative thickness of the wall (before treatment 0.41 ± 0.07 , after 0.41 ± 0.07 , $P = 0.871$), as well as in the left ventricular mass index (before treatment 122.29 ± 37.36 g/m², after 118.00 ± 31.00 g/m², $P = 0.849$).

The specific gravity of patients with eccentric left ventricular hypertrophy after a year of treatment increased from 32 % ($n = 10$) to 39 % ($n = 12$) ($P = 0.5668$), with concentric hypertrophy decreased from 42 % ($n = 13$) to 39 % ($n = 12$) ($P = 0.8107$), with normal left ventricular geometry went from 19 % ($n = 6$) to 16 % ($n = 15$) ($P = 0.7570$), however, none of the changes reached the statistical probability limit. The number of patients with AH with the concomitant subclinical hypothyroidism with signs of concentric left ventricular remodeling remained unchanged – 6 % ($n = 2$) before treatment, 6 % ($n = 2$) after.

Analysis of the left ventricular diastolic function indices revealed no significant effect of the antihypertensive therapy with statin supplementation in patients with AH and a concomitant subclinical hypothyroidism on the end-diastolic pressure level; (E/e' before treatment 7.98 ± 2.7 , after treatment 8.04 ± 2.46 ; $P = 0.871$), on the ratio of the early left ventricular filling velocity to the velocity of atrial systole (E/A before treatment 0.86 ± 0.32 , after treatment 0.81 ± 0.28 ; $P = 0.545$), on the mean pulmonary artery pressure (before treatment 16.29 ± 5.08 mm Hg, after treatment 15.81 ± 4.98 mm Hg, $P = 0.686$).

The study of left ventricular diastolic filling types in dynamics revealed a tendency towards a decrease in the specific gravity of patients with "normal" type of filling of the left ventricle from 10 % ($n = 3$) to 6 % ($n = 2$) ($P = 0.5638$), with "pseudonormal" filling from 19 % ($n = 6$) to 16 % ($n = 5$) ($P = 0.7570$), and to an increase of the percentage of patients with the left ventricular filling type "impaired relaxation" from 71 % ($n = 22$) to 77 % ($n = 24$), ($P = 0.5922$). No patients with a restrictive left ventricular filling type were registered.

Transvalvular peak pressure gradients also did not change significantly under the influence of treatment: transmitral ($P = 0.587$), transaortic ($P = 0.563$), transicuspid ($P = 0.509$), transpulmonary ($P = 0.256$).

The influence of the statin therapy on vascular remodeling in patients of this group was characterized by a tendency towards a decrease in thickness of the intima-media complex of the right (0.769 ± 0.276 mm vs. 0.701 ± 0.222 mm, $p = 0.512$) and left (0.759 ± 0.185 mm vs. 0.745 ± 0.179 mm, $P = 0.978$) common carotid arteries.

Discussion

Data of literature sources and the results of our own studies regarding the dependence of indices of the heart structure and function in patients with arterial hypertension on the negative impact of subclinical hypothyroidism were described by us in the previous works [34], including the analysis of the effect of statins on the indices of 24h-blood pressure monitoring and their changes after a long-term intake by patients of this category [35,36].

In the study [37], researchers analyzed the effect of SH on the diastolic function of the left ventricle by studying changes in time intervals with the help of a pulsed-wave Doppler. A similar analysis is complemented by the data of pulsed-wave tissue Doppler imaging in the publication [38]. Analyzing the modifying effect of hypothyroidism on cardiovascular pathology, the authors of the last publication point to the important changes in the structure and function of the heart, particularly in the diastolic function, in patients with hypothyroidism, the severity of which depends, according to the researchers, on the severity and duration of the thyroid hormone deficit. Similar results were also obtained with the help of modern diagnostic methods – magnetic resonance imaging and radionuclide ventriculography [39], which coincide with the data obtained by us.

However, there is a lack of information regarding the influence of statin therapy on the heart and blood

vessels in patients with arterial hypertension combined with SH. The results of our studies strongly suggest that the presence of a concomitant subclinical hypothyroidism in patients with AH significantly affects structural and geometric remodeling of the heart and blood vessels, which, along with the disorders of lipid metabolism, are a basis for prescription of statins to the patients in this category. In patients with AH and a concomitant SH, there was an inhibition of the processes of reverse pathological remodeling of the left ventricle observed on the background of antihypertensive therapy, even provided the addition of statins to the therapeutic regimens.

Achievement of the target level of blood pressure according to 24h-BPM in 75 % of patients with AH with subclinical hypothyroidism on the background of antihypertensive therapy with the addition of statins was not accompanied by a significant reduction in the cavity size, wall thicknesses, LV mass, improvement of the diastolic filling and systolic function, decrease in the thickness of intima-media complex [36,37]. The data obtained allow us to consider a concomitant subclinical hypothyroidism in patients with AH as a negative factor of additional cardiovascular risk, which should be taken into a consideration when prescribing therapy.

Conclusions

1. In patients with AH with a concomitant subclinical hypothyroidism, the antihypertensive therapy carried out during the year using first-line drugs with addition of atorvastatin is accompanied by an achievement of target level of SBP in the active period of the day in 75 %, in the passive period – in 65 % of patients (according to the 24h-BPM data).

2. Achievement of the target level of blood pressure in patients with AH with subclinical hypothyroidism on the background of antihypertensive therapy with addition of statins was not accompanied by a significant reduction in cavity sizes, wall thicknesses, LV mass, improvement in LV diastolic filling, and decrease in the thickness of intima-media complex.

Prospects for further studies are to investigate the effect of statin therapy as well as hormone replacement therapy on the structural-geometric and functional parameters of the heart and blood vessels in patients with AH with a concomitant subclinical hypothyroidism.

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