

CEREBROVASCULAR REACTIVITY IN PATIENTS WITH A COMBINATION OF RHEUMATOID ARTHRITIS AND HYPERTENSION

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Annotation.

Cardiovascular diseases are the leading causes of death and disability worldwide. Currently, the contribution of comorbid conditions to the development and progression of cardiovascular pathology is being actively studied. It has been proven that rheumatoid arthritis (RA) acts as an independent risk factor in the development of cardiovascular complications, including cerebral strokes.

Purpose – To investigate cerebrovascular reactivity (CVR) depending on rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) positivity in hypertensive patients with rheumatoid arthritis (RA).

Material and methods – A single cross-sectional study included 61 patients (mean age 59.8 ± 7.7 years; 6 men and 55 women) with combined RA and grade 1–2 hypertension (HTN). The duration of RA was 11.2 ± 7.4 years.

The duration of HTN was 12.1 ± 8.6 years. All patients were treated with methotrexate. RA patients were categorized into RF/ACPA seronegative and RF/ACPA seropositive subgroups. CVR was evaluated by bilateral transcranial Doppler sonography of the middle cerebral arteries (MCA) in a hyperoxic test (O₂CVR) and in a hypercapnic test (CO₂CVR). We measured MCA mean blood flow velocity (V_{mn}), time average maximal blood flow velocity (TAMX), peak systolic velocity (V_{ps}) at baseline, within 2 minutes of 100% oxygen inhalation and within 3 minutes of recovery phase (hyperoxic test). We calculated the following indicators for assessing CVR: index changes of flow velocity mean (IFV_m), speed modification of velocity (SMFV_m) and normalized answer of reserve (NAR). Then, according to the same scheme, we performed a hypercapnic test with the inhalation of a 4% mixture of carbon dioxide with air. Values are presented as Me [Q1; Q3].

Results – Hypertensive patients with RA had a decrease in response power of MCA blood flow to hyperoxia. RF-seropositive RA patients had a more pronounced decrease in the power of the response to hyperoxia compared with RF-seronegative RA patients. The values of IFV_m in the hyperoxic test were $-13.4 [-19.9; -0.9]$ versus $-16.2 [-22.7; -13.4]\%$ ($p=0.0453$), respectively. ACPA-seropositive RA patients had not only a more pronounced decrease in the power of the response of MCA blood flow to hyperoxia, but also a more pronounced slowdown in the response velocity of MCA blood flow to hyperoxia compared with ACPA-seronegative RA patients. The values of IFV_m in the hyperoxic test were $-9.74 [-15.9; 2.84]$ versus $-20.9 [-25.0; -14.7]\%$ ($p=0.0062$), the values of SMFV_m were $-0.05 [-0.09; 0.02]$ versus $-0.09 [-0.20; -0.05]$ sm/s² ($p=0.0488$) respectively. Combined RA and HTN patients had a decrease in response power of MCA blood flow to hypercapnia. However, no statistical differences were found in the state of CO₂CVR between patients with seropositive RA and seronegative RA.

Conclusion – Hypertensive patients with seropositive RA have a more pronounced O2CVR disorder in compared to seronegative RA patients.

Keywords: cerebrovascular reactivity, rheumatoid arthritis, hypertension, rheumatoid factor, anti-citrullinated protein antibody

REVMATOID ARTRIT VA ARTERIAL GIPERTENZIYA KOMBINATSIYASI BO'LGAN BEMORLARDA SEREBROVASKULYAR REAKTIVLIK

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Annotatsiya.

Kardiovaskulyar kasalliklar butun dunyo bo'ylab o'lim va nogironlik sabablari tarkibida etakchi o'rinni egallaydi. Hozirgi vaqtda komorbid holatlarning kardiovaskulyar patologiyaning rivojlanishi va rivojlanishiga qo'shgan hissi faol o'rganilmoqda. Romatoid artrit (ra) yurak-qon tomir asoratlari, shu jumladan miya qon tomirlari rivojlanishida mustaqil xavf omili ekanligi isbotlangan.

Maqsad – Romatoid omil (RF) seropozitivligi va tsiklik sitrullinlangan peptid (ACCP) antikorlariga qarab Romatoid artrit (ra) va arterial gipertenziya (ah) kombinatsiyasi bo'lgan bemorlarda serebrovaskulyar reaktivlik (CVD) holatini o'rganish.

Material va usullar – Bir vaqtning o'zida o'tkazilgan tadqiqotga 1-2 darajali ra va ah kombinatsiyasi bilan 61 bemor (6 erkak va 55 ayol) kiritilgan (o'rtacha yoshi $59,8 \pm 7,7$ yosh). Tekshirilayotgan sub'ektlarda ra davomiyligi o'rtacha $11,2 \pm 7,4$ yilni, AG davomiyligi $12,1 \pm 8,6$ yilni tashkil etdi. Barcha bemorlarga metotreksat berildi. Rossiya federatsiyasi va ACCP mavjudligiga qarab, bemorlar Rossiya federatsiyasi-/ACCP-seropozitiv va Rossiya federatsiyasi-/ ACCP-seronegativ ra bilan kichik guruhlariga bo'lingan. TSVRNI baholash uchun giperoksik va giperkapnik testlarni o'tkazish bilan o'rta miya arteriyalarining (sma) transkraniyal dopplerografiyasi o'tkazildi. O'rtacha (V_{mn} , sm/s), o'rtacha maksimal (TAMAX, sm/s) va eng yuqori sistolik (VPS, sm/s) dam olish paytida sma ga qon oqimining tezligi 2 daqiqa davomida 100% kislorod bilan nafas olish va 3 daqiqa tiklanish bosqichida (giperoksik sinov) o'lchandi. Keyin xuddi shu sxema bo'yicha karbonat angidridning 4% aralashmasini havo bilan inhalatsiyalash amalga oshirildi (giperkapnik sinov). CVPNI baholash uchun qon oqimi tezligining nisbiy o'zgarish koeffitsienti (Kisotn), qon oqimining chiziqli tezligining (LSC) o'zgarishining sinov tezligi (TSI) va LSCNI tiklash indeksi hisoblab chiqilgan. Ma'lumotlar Me [Q1; Q3] shaklida taqdim etilgan.

Natijalar – Giperoksik testda ra va ah bilan og'riqan bemorlarda sma tarkibidagi qon oqimining stimulg javob berish kuchining pasayishi kuzatildi, bu Rossiya federatsiyasi bilan seropozitiv ra bilan Rossiya federatsiyasi bilan taqqoslaganda seronegativ. Kisotn mos ravishda $-13,4\%$ [-19,9; -0,9] va $-16,2\%$ [-22,7; -13,4] ni tashkil etdi ($p=0,0453$). ACC-musbat ra bo'lgan bemorlarda ACC-salbiy ra bo'lgan bemorlarga nisbatan Kisotn (mos ravishda $-9,74\%$ [-15,9; 2,84] va $-20,9\%$ [-25,0; -14,7]; $p \setminus U003D 0,0062$), shuningdek TSI Lsk ($-0,05$ sm / S2 [-0,09; 0,02] va $-0,09$ sm/C2 [-0,20; -0,05] mos ravishda; $p \setminus u003d 0,0488$). GIPERKAPNIK testda ra va ah kombinatsiyasi bo'lgan barcha bemorlarda miya qon oqimining giperkapniyaga javob kuchining pasayishi kuzatildi. Shu bilan birga, seropozitiv va

seronegativ ra bo'lgan bemorlarda wdh holatidagi statistik jihatdan sezilarli farqlar aniqlanmagan.

Xulosa – Rossiya federatsiyasi va ACCPDA seropozitiv bo'lgan ah va ra bilan og'riqan bemorlarda GIPEROKSIK namunada CVP parametrlarining buzilishi Rossiya federatsiyasi va ACCPDA seronegativ bemorlarga nisbatan ko'proq namoyon bo'ladi.

Kalit so'zlar: serebrovaskulyar reaktivlik, revmatoid artrit, arterial gipertenziya, revmatoid omil, tsiklik sitrullinlangan peptidga antikorlar

ЦЕРЕБРОВАСКУЛЯРНАЯ РЕАКТИВНОСТЬ У ПАЦИЕНТОВ С СОЧЕТАНИЕМ РЕВМАТОИДНОГО АРТРИТА И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Аннотация.

Кардиоваскулярные болезни лидируют в структуре причин смертности и инвалидизации во всем мире. В настоящее время активно изучается вклад коморбидных состояний в развитие и прогрессирование кардиоваскулярной патологии. Доказано, что ревматоидный артрит (РА) выступает в качестве независимого фактора риска в развитии кардиоваскулярных осложнений, в том числе и мозговых инсультов.

Цель исследования – Изучить состояние цереброваскулярной реактивности (ЦВР) у пациентов с сочетанием ревматоидного артрита (РА) и артериальной гипертензии (АГ) в зависимости от серопозитивности по ревматоидному фактору (РФ) и антителам к циклическому цитруллинированному пептиду (АЦЦП).

Материал и методы – В одномоментное исследование включен 61 пациент (6 мужчин и 55 женщин) с сочетанием РА и АГ 1–2-й степени (средний возраст – $59,8 \pm 7,7$ года). Продолжительность РА у обследуемых составила в среднем $11,2 \pm 7,4$ года, продолжительность АГ – $12,1 \pm 8,6$ года. Все пациенты получали метотрексат. В зависимости от наличия РФ и АЦЦП пациенты были разделены на подгруппы с РФ-/АЦЦП-серопозитивным и РФ-/АЦЦП-серонегативным РА. Для оценки ЦВР выполняли транскраниальную доплерографию среднемозговых артерий (СМА) с проведением гипероксической и гиперкапнической проб. Измеряли среднюю (V_{mn} , см/с), усредненную по времени максимальную ($TAMAX$, см/с) и пиковую систолическую (V_{ps} , см/с) скорости кровотока в СМА в состоянии покоя, в течение 2 минут ингаляции 100%-го кислорода и 3 минут фазы восстановления (гипероксическая проба). Затем по этой же схеме проводили ингаляцию 4%-й смеси углекислого газа с воздухом (гиперкапническая проба). Для оценки ЦВР рассчитывали коэффициент изменения скорости кровотока относительный (КИСотн), тестовую скорость изменения (ТСИ) линейных скоростей кровотока (ЛСК) и индекс восстановления ЛСК. Данные представлены в виде $Me [Q1; Q3]$.

Результаты – В гипероксической пробе у пациентов с РА и АГ наблюдалось уменьшение силы ответной реакции кровотока в СМА на стимул, более выраженное в группе с РФ-серопозитивным РА по сравнению с РФ-серонегативным. КИСотн составил $-13,4\% [-19,9; -0,9]$ и $-16,2\% [-22,7; -13,4]$ соответственно ($p=0,0453$). У

пациентов с АЦЦП-положительным РА по сравнению с пациентами с АЦЦП-отрицательным РА выявили более выраженное уменьшение КИСотн ($-9,74\%$ [$-15,9; 2,84$] и $-20,9\%$ [$-25,0; -14,7$] соответственно; $p=0,0062$), а также ТСИ ЛСК ($-0,05$ см/с² [$-0,09; 0,02$] и $-0,09$ см/с² [$-0,20; -0,05$] соответственно; $p=0,0488$). В гиперкапнической пробе у всех пациентов с сочетанием РА и АГ также наблюдали снижение силы ответной реакции мозгового кровотока на гиперкапнию. Однако статистически значимых различий в состоянии ЦВР у пациентов с серопозитивным и серонегативным РА не выявлено.

Заключение – Серопозитивные по РФ и АЦЦП пациенты с АГ и РА имеют более выраженные нарушения параметров ЦВР в гипероксической пробе по сравнению с пациентами серонегативными по РФ и АЦЦП.

Ключевые слова: цереброваскулярная реактивность, ревматоидный артрит, артериальная гипертензия, ревматоидный фактор, антитела к циклическому цитруллинированному пептиду

Introduction. Cardiovascular diseases are the leading causes of death and disability worldwide. Currently, the contribution of comorbid conditions to the development and progression of cardiovascular pathology is being actively studied. It has been proven that rheumatoid arthritis (RA) acts as an independent risk factor in the development of cardiovascular complications, including cerebral strokes. Thus, in patients under the age of 50 suffering from RA, the risk of ischemic stroke was increased by 1.64 times (95% confidence interval (95% CI): 1.23- 2.05), and hemorrhagic stroke – by 1.68 times (95% CI: 1.11–2.53) compared to the general population [1]. The presence of arterial hypertension (AH) in patients with RA, the risk of recurrent stroke increases (risk ratio (HR) – 1.37; 95% CI: 1.12–1.67), especially ischemic stroke and transient ischemic attacks (HR=1.41; 95% CI: 1.13–1.74) during the 6-year follow-up period [2].

Hypertension undoubtedly plays a major role in the pathogenesis of disorders of the mechanisms of autoregulation of cerebral circulation, which ensure the constancy of cerebral blood flow through the complex interaction of neurohumoral, myogenic and endothelial vascular tone regulation systems [3, 4]. In the work of M. Liu et al. [5] It has been shown that cerebrovascular reactivity (CVR) is a more reliable predictor of stroke in patients who have suffered an acute ischemic event, compared with the severity of stenosis of

the internal carotid and middle cerebral arteries. In this regard, early diagnosis of functional and potentially reversible CVR disorders is one of the priorities in the prevention of cerebral stroke.

The increase in the frequency of cardiovascular complications in RA is due not only to traditional risk factors, but also to the influence of a systemic autoimmune inflammatory process leading to hyperproduction of proinflammatory cytokines and autoantibodies, activation of the sympatho-adrenal and renin-angiotensin-aldosterone systems [6]. It has been established that rheumatoid factor seropositivity (RF) is accompanied by an increase in cardiovascular risk already at the onset of RA [7]. At the same time, the presence of RF is associated with an increase in mortality from cardiovascular diseases even after correction of risk factors, including in patients without joint symptoms [8]. The presence of antibodies to cyclic citrullinated peptide (ACCP) is characterized by a more severe course of RA, rapid progression of the erosive and destructive process in the joints, and a high risk of developing extra-articular manifestations. The relationship between ADC positivity and the risk of coronary heart disease (CHD) has also been proven (odds ratio (OR) – 2.8; 95% CI: 1.19–6.56; $p=0.009$) [9] and the presence of endothelial dysfunction [10].

Information on the state of CVR in patients with RA against the background of both normal blood pressure (BP) and hypertension is scarce and limited to earlier work by our scientific group [11]. In connection with the above, the aim of the study was to study the state of cerebrovascular reactivity in patients with a combination of rheumatoid arthritis and hypertension, depending on the seropositivity for rheumatoid factor and antibodies to cyclic citrullinated peptide.

Research materials and methods. The simultaneous study included 61 patients (6 men and 55 women; average age – 59.8 ± 7.7 years) with a combination of RA and hypertension of the 1st-2nd degree, who were observed

in Clinics of the Federal State Budgetary Educational Institution of the Siberian State Medical University of the Ministry of Health of the Russian Federation in the period from 2013 to 2018. All patients signed informed consent prior to the start of the study. A comprehensive clinical and laboratory-instrumental examination was conducted to verify the diagnosis, exclude secondary forms of hypertension, determine a combination of risk factors and clarify the condition of target organs. Criteria for inclusion in the study: combination of RA (diagnostic criteria of the American College of Rheumatology/European Alliance of Rheumatology Associations (ACR/EULAR, American College of Rheumatology/European Alliance of Associations for Rheumatology) 2010) and essential hypertension of the 1st-2nd degree (recommendations for the diagnosis and treatment of hypertension of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH, European Society of Cardiology/ European Society of Hypertension) 2013); age 38–70 years; methotrexate therapy. Exclusion criteria from the study: the presence of symptomatic hypertension, a history of stroke, atherosclerosis of the brachiocephalic arteries with stenosis $\geq 50\%$, coronary heart disease, diabetes mellitus, severe comorbid pathology requiring regular medication; lack of informed consent of the patient to conduct the study.

The duration of RA was on average 11.2 ± 7.4 years, the duration of hypertension is 12.1 ± 8.6 years. These were mainly patients with an average degree of activity (3.2 ± 1.0 according to DAS-28 (Disease Activity Score 28)) and III–IV X-ray stage; 72% of patients had seropositive IgM-RF and ADC RA. Approximately one third (36%) of patients had extra-articular manifestations, mainly rheumatoid nodules. All patients received methotrexate. Selective nonsteroidal anti-inflammatory drugs and glucocorticoids were taken by 53% and 20% of patients, respectively. Dyslipidemia was found in 92%, obesity – in 44%, impaired glucose tolerance – in 31%, carotid artery atherosclerosis with stenosis less than 30% – in 65% of cases.

In order to assess the effect of RA-associated factors on CVR parameters, we divided the entire sample into subgroups depending on the seropositivity of IgM-RF and ADC.

These groups were comparable in clinical characteristics and antirheumatic therapy. To assess CVR, transcranial dopplerography of the medial cerebral arteries (SMA) was performed with hyperoxic and hypercapnic tests. The average (V_{mn} , cm/s), time-averaged maximum (TAMAX, cm/s), peak systolic (V_{ps} , cm/s) and final diastolic (V_{ed} , cm/s) were measured the velocity of blood flow in the SMA at rest, during 2 minutes of inhalation of 100% oxygen and within 3 minutes of the recovery phase (hyperoxic test). Then, according to the same scheme, inhalation of a 4% mixture of carbon dioxide with air was performed (hypercapnic test). To assess the phase of the cerebrovascular reserve, the relative coefficient of change in blood flow velocity (KISotn), reflecting the strength of the response to the stimulus, and the test rate of change (TSI) of linear blood flow velocities (LSC), reflecting the rate of response to the stimulus, were calculated; to assess the phase of autoregulation of cerebral blood flow, the LSC recovery index (IV) is used, reflecting the restoration of blood flow after cessation of exposure.

The data obtained were processed in accordance with the rules of variation statistics using the Statistica for Windows 10.0 software (StatSoft Inc., USA). The analysis of qualitative features was carried out using the exact Fisher criterion. The compliance of the sample with the normal distribution law was checked by the Kolmogorov–Smirnov agreement criterion. Quantitative data obeying the normal distribution law were presented in the form of $M \pm SD$, where M is the arithmetic mean, SD is the standard deviation; quantitative data that do not obey the normal distribution law are in the form of median (Me) and quartiles ($Q1$; $Q3$). The statistical significance of intergroup differences in mean values was assessed using the Student's t-test in the case of a normal distribution of data; in all other cases, differences between independent groups

were analyzed using the nonparametric Mann–Whitney U-test. The results of the statistical analysis were considered statistically significant at $p < 0.05$.

The results and their discussion. During the hypoxic test, 56% of the subjects had a violation of the cerebrovascular reserve phase with a decrease in strength ($KISSOTN = 12.9 = 10.3\%$) and the rate of reaction of blood flow in the SMA to hyperoxia ($(((QI LSK = 0.09 = 0.08 \text{ cm/s}^2)$). The indices of the cerebral blood flow recovery phase corresponded to normal values (And in LSC $= 1.03 = 0.11$). In the hypercapnic test, 66% of the subjects also showed a reduced response of cerebral blood flow to the stimulus ($KISSOTN = 43.0 \pm 18.9\%$). The rate of response to hypercapnia ($(QI LSC = 0.3 = 0.16 \text{ cm/s}^2)$) and the phase of restoration of blood flow after cessation of inhalation (And in LSC $= 1.07 = 0.11$) were within the normal range. When studying the relationship between the immunological signs of RA and the parameters of the reactivity of cerebral vessels in patients with RA in combination with hypertension, we obtained the following results. In the group with hypertension and RF-positive RA, compared with RF-negative RA, there was a more pronounced decrease in acidosis ($p = 0.0453$), which indicates a decrease in the strength of the blood flow response to hyperoxia. In patients with ADCP-positive RA, lower values of $CYSotn$ ($p = 0.0062$) and $TSI LSC$ ($p = 0.0488$) were observed compared with ADCP-negative RA, which reflects a decrease in the strength and speed of the blood flow reaction to oxygen inhalation. According to the results of the hypercapnic test, there were no statistically significant differences in CVR parameters in patients with seropositive and seronegative RA.

Conclusions. The data we obtained on the state of CVR in patients with a combination of RA and AH are consistent with the results of studies on the assessment of CVR in patients with AH without RA. Already in the early stages of the disease, a decrease in the functional reserve of cerebral circulation is recorded in patients with hypertension [12]. In patients with hypertension, compared with healthy volunteers, there is a statistically significant decrease in

the strength and speed of responses to hyperoxia and the absence of impaired response to hypercapnia [13].

The features of the CVR condition in patients with a combination of RA and hypertension, depending on the immunological parameters – the presence of RF and ADC – have not been previously described. For the first time, we showed the presence of statistically significantly more pronounced violations of the cerebrovascular reserve phase in hyperoxia in a subgroup of patients with RA and AG, seropositive for the Russian Federation and/or ADC. The mechanisms of autoregulation of cerebral blood flow in the recovery phase with a combination of RA and hypertension seem to remain intact, which is confirmed by the normal values of blood flow parameters in the SMA.

As is known, ADC-positive RA is associated with the carrier of the antigen of the main histocompatibility complex class II (HLA II) HLA-DR1 (and DR4), which has more than 22 alleles. It is established that the carrier HLA-DRB1*0404 is associated not only with a higher risk of extra-articular manifestations in RA, but also with the development of endothelial dysfunction, the leading mechanism of pathogenesis of damage to the cardiovascular system [14, 15]. According to the literature, one of the possible causes of impaired cerebral perfusion in RA, especially in the presence of hypertension, is brain damage by the type of cerebral small vessel disease. It includes pathological processes of various etiologies in the microcirculatory vessels of the brain, and endothelial dysfunction plays a leading role in the genesis of these disorders [16, 17].

Our data on the adverse effects of RF and ADC on the condition of CVR in patients with a combination of RA and hypertension are consistent with a new paradigm, according to which systemic inflammation is of great importance in the development and progression of cardiovascular complications in patients with RA. Moreover, the results obtained coincide with the opinion of EULAR experts, who suggested taking into account

seropositivity in the Russian Federation and/or ADC in determining the prognosis of cardiovascular events in patients with RA. RA and AH have common links in immunopathogenesis: inflammatory mediators; posttranslational modifications of peptides/proteins with subsequent immune responses; qualitative and quantitative changes in lipoproteins; increased activity of oxidative stress; endothelial dysfunction [18,19]. Posttranslational modifications of proteins in RA serve as targets for autoantibodies, which can have harmful effects on the cardiovascular system and increase systemic/local inflammation. Oxidative stress resulting from inflammation, in turn, directly affects endothelial function. The pathogenesis mechanisms associated with RA exacerbate the negative effects of traditional cardiovascular risk factors, in particular hypertension, negatively affect each other, are integrated into a single pathological process, which leads to an increase in the frequency of cardiovascular complications in rheumatological patients [20]. In this regard, the presence of RF and ADC undoubtedly worsens the prognosis of patients with RA in combination with hypertension and requires careful monitoring of the structural and functional state of the cardiovascular system, including cerebral blood flow, and correction of both traditional risk factors for cardiovascular diseases and factors associated with inflammatory activity and characteristic of RA immunological disorders.

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