DOI: 10.20514/2226-6704-2021-11-4-284-291 УДК 616.711-002-06:[616.13-004.6:616155.194]

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АНЕМИЯ У ПАЦИЕНТОВ С АКСИАЛЬНЫМИ СПОНДИЛОАРТРИТАМИ НЕ АССОЦИИРОВАНА С УВЕЛИЧЕНИЕМ РИГИДНОСТИ СОСУДИСТОЙ СТЕНКИ И ТОЛЩИНЫ КОМПЛЕКСА ИНТИМА-МЕДИА (РЕЗУЛЬТАТЫ ОДНОЦЕНТРОВОГО КРОСС-СЕКЦИОННОГО ИССЛЕДОВАНИЯ)

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Anemia in Patients with Axial Spondyloarthritis is Not Associated with an Increase of Arterial Stiffness and Intima-Media Thickness (Results of a Single-Center Cross-Sectional Study)

Резюме

Цель — изучение показателей ригидности сосудистой стенки и субклинического атеросклероза у пациентов с аксиальными спондилоартритами (аксСпА) без клинически манифестной кардиоваскулярной патологии в зависимости от наличия анемии. **Материал и методы.** Включены 102 пациента с аксСпА, возраст — 37,7±9,8 лет, длительность аксСпА — 13,5±8,7 лет, 66 (64,7%) мужчин. Рассчитаны индексы BASDAI, ASDAS-СРБ, исследованы гемограмма, скорость оседания эритроцитов (СОЭ), уровень С-реактивного белка (СРБ). Исследование параметров артериальной ригидности проводили методами осциллографии и фотоплетизмографии, оценка толщины комплекса интима-медиа (ТКИМ) осуществляли в ходе ультразвукового исследования в В-режиме согласно стандартным протоколам. **Результаты.** В ходе анализа свойств пульсовой волны статистически значимых различий показателей ригидности сосудистой стенки у пациентов аксСпА с наличием и без анемического синдрома не обнаружено. У пациентов с анемией скорость распространения пульсовой волны в аорте (PWVao) составила 7,4±1,5 м/с, индекс аугментации в аорте (Aix-ao) — 19,1±13,7%, индекс жесткости (SI) — 8,2±1,7 м/с, у пациентов без анемии — 7,4±1,4 м/с, 17,3±10,6% и 8,8±2,0 м/с, соответственно (p >0,05 для всех). Средние значения ТКИМ у пациентов с анемией составили 0,70±0,13 см, у па-

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циентов без анемии — 0,73±0,16 (p >0,05). По результатам корреляционного анализа установлены взаимосвязи между Aix-ao, PWVao, SI, ТКИМ и возрастом пациентов (r=0,488, r=0,516, r=0,289, r=0,461, соответственно, p <0,05), взаимосвязи между Aix-ao, PWVao и клиническим индексом активности BASDAI (r=0,243, r=0,253, соответственно, p <0,05). Выявлены взаимосвязи между PWVao и Aix-ao (r=0,442, p <0,001), SI (r=0,273, p=0,011) и ТКИМ (r=0,236, p=0,034). **Заключение.** В ходе настоящего исследования не подтверждено отрицательное влияние анемии на показатели ригидности сосудистой стенки и ТКИМ у пациентов с аксСпА. Полагаем, что это связано с потенциальным протективным эффектом анемии, обусловленным общеизвестными патофизиологическими паттернами — снижением вязкости крови и индукцией синтеза оксида азота. Требуется дальнейшее изучение взаимосвязей между уровнем гемоглобина и маркерами эндотелиальной дисфункции у пациентов с воспалительными заболеваниями позвоночника.

Ключевые слова: *анемия, гемоглобин, атеросклероз, артериальная ригидность, толщина комплекса интима-медиа, анкилозирующий спондилит, аксиальный спондилоартрит*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 13.05.2021 г.
Принята к публикации 28.07.2021 г.

Для цитирования: Сафарова К.Н., Махина В.И., Дорогойкина К.Д. и др. АНЕМИЯ У ПАЦИЕНТОВ С АКСИАЛЬНЫМИ СПОНДИЛОАРТРИТАМИ НЕ АССОЦИИРОВАНА С УВЕЛИЧЕНИЕМ РИГИДНОСТИ СОСУДИСТОЙ СТЕНКИ И ТОЛЩИНЫ КОМПЛЕКСА ИНТИМА-МЕДИА (РЕЗУЛЬТАТЫ ОДНОЦЕНТРОВОГО КРОСС-СЕКЦИОННОГО ИССЛЕДОВАНИЯ). Архивъ внутренней медицины. 2021; 1(4): 284-291. DOI: 10.20514/2226-6704-2021-11-4-284-291

Abstract

Aim: to study parameters of arterial stiffness and subclinical atherosclerosis in patients with axial spondyloarthritis (axSpA) without clinically manifest cardiovascular pathology depending on the presence of anemia. **Material and methods.** 102 patients with axSpA (mean age — 37.7±9.8 years, axSpA duration — 13.5±8.7 years, 66 (64.7%) men) were included. The BASDAI index and C-reactive protein (CRP)-based ASDAS score were measured, the hemogram, the erythrocyte sedimentation rate (ESR), and the level of CRP were studied. Parameters of arterial stiffness were studied by oscillography and photoplethysmography, intima-media thickness (IMT) was evaluated by B-mode ultrasound according to standard protocols. **Results.** During analysis of pulse wave properties, no statistically significant differences in parameters of vascular wall stiffness were found in axSpA patients with and without anemia. Aortic pulse wave velocity (PWVao) in patients with anemia was 7.4±1.5 m/sec, aortic augmentation index (Aix-ao) was 19.1±13.7%, stiffness index (SI) was 8.2±1.7 m/sec; in patients without anemia — 7.4±1.4 m/sec, 17.3±10.6% and 8.8±2.0 m/sec, respectively (p >0.05 for all). IMT in patients with anemia was 0.70±0.13 cm, in patients without anemia — 0.73±0.16 cm (p >0.05). Correlation analysis was performed and significant correlations were noted between Aix-ao, PWVao, SI, IMT and age (r=0.488, r=0.516, r=0.289, r=0.461, respectively, p <0.05); Aix-ao, PWVao and the BASDAI index (r=0.243, r=0.253, respectively, p <0.05). Significant correlations between PWVao and Aix-ao (r=0.442, p <0.001), SI (r=0.273, p=0.011) and IMT (r=0.236, p=0.034) were found. **Conclusion.** The present study did not confirm the negative effect of anemia on vascular wall stiffness parameters and IMT in patients with axSpA. We consider that potential protective effect of anemia, due to well-known pathophysiological patterns — a decrease in blood viscosity and the induction of nitric oxide synthesis, plays an important role. Further studies are required to assess relationship between hemoglobin levels and markers of endothelial dysfunction in patients with axSpA.

Key words: *anemia, hemoglobin, atherosclerosis, arterial stiffness, intima-media thickness, ankylosing spondylitis, axial spondyloarthritis*

Conflict of interest

The authors declare that this work, its subject, subject and content do not affect competing interests. Source of financing

Sources of funding

The authors claim that there is no funding for the study

Article received 13.05.2021.
Accepted for publication 28.07.2021

For citation: Safarova K.N., Makhina V.I., Dorogoykina K.D. et al. Respiratory rehabilitation for post-COVID-19 patients. The Russian Archives of Internal Medicine. 2021; 11(4): 284-291. DOI: 10.20514/2226-6704-2021-11-4-284-291

Aix-ao — aortic augmentation index, axSpA — axial spondyloarthritis, CRP — C-reactive protein, ESR — erythrocyte sedimentation rate, IMCT– intima-media complex thickness, PWVao — pulse wave velocity of the aorta, SI — stiffness index

Introduction

Axial spondyloarthritis (axSpA) is a group of chronic autoimmune diseases with predominant damage to the axial skeleton (spine and/or sacroiliac joints), the possible involvement of peripheral joints, enthesis, skin (psoriasis), intestines (Crohn's disease, ulcerative colitis), eyes (uveitis), heart and aorta [1]. The development of a chronic autoinflammatory status is considered the main predictor of the early development and progression of cardiovascular diseases in patients with axSpA.

The risk of cardiovascular diseases in cases of axSpA is 1.3-1.5 times higher than in the general population, while mortality due to unfavorable cardiovascular events is 20-40% higher than in the general population [2–4].

Anemia is a common comorbid disease in patients with axSpA [5–7]. Persistent systemic inflammation underlying the impairment of iron metabolism and dysfunction of erythropoiesis is also a leading cause of endothelial dysfunction, increased arterial stiffness, early development and progression of atherosclerotic lesions of the vascular wall [8].

A number of studies [9–11] describe increased arterial stiffness in patients with axSpA compared with healthy individuals. The effect of anemia on the processes of vascular wall remodeling and arterial stiffness parameters is generally understudied, and there are currently no data on the correlation between anemia and damage to arterial vessels in patients with axSpA. In this regard, it is of practical interest to study the parameters indicating changes in the rigidity of the arterial wall in patients with axSpA with and without anemia.

The **study objective** was to investigate the parameters of vascular wall rigidity and subclinical atherosclerosis in patients with axSpA without clinically manifesting cardiovascular disease, depending on the presence of anemia.

Materials and methods

The study included 102 patients with axSpA (age — 37.7±9.8 years, duration of axSpA — 13.5±8.7 years, 66 (64.7%) male subjects) who were hospitalized at the Regional Clinical Hospital (Saratov) in 2017-2020. Inclusion criteria were the following: compliance with axSpA criteria of the Assessment of Spondyloarthritis International Society, 2009 [12], age ³18, signed informed consent to participate in the study. The study did not include patients with coronary heart disease (exertional angina, previous myocardial infarction, chronic heart failure), uncontrolled arterial hypertension, atherosclerotic plaques according to duplex examination of carotid arteries, chronic kidney disease of stages 3-5, liver failure, viral hepatitis, HIV infection, tuberculosis, chronic diseases in acute phase (peptic ulcer, cholecystitis), cancer and lymphoproliferative diseases, and pregnant women.

Standard parameters of CBC and blood biochemical assay, concentration of C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were determined. Estimated glomerular filtration rate (eGFR) was defined using the CKD-EPI formula (Chronic Kidney Desease Epidemiology Collaboration, 2009) [13]. BASDAI (the Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (the Ankylosing Spondylitis Disease Activity Score) indices using CRP were calculated to determine the activity of axSpA.

Clinical features of the examined patients are presented in Table 1. Patients were comparable in age and disease duration. However, the percentage of female patients and the number of patients positive for HLA-B27 were higher among patients with axSpA and anemia. Patients with anemia more often received therapy with synthetic and/or biological disease-modifying drugs in comparison with patients without it. The percentage of patients receiving non-steroidal anti-inflammatory drugs and systemic glucocorticoids demonstrated no statistically significant difference.

Table 1. *The main clinical and demographic parameters and characteristics of drug treatment in patients with axSpA included in the study*

Parameter	All patients with axSpA (n=102)		p
	Without anemia (n = 50) M±SD / n (%)	With anemia (n = 52) M±SD / n (%)	
Age, years	37,0±9,6	38,5±10,0	0,454
Men	40 (80)	26 (50)	0,002*
Duration of axSpA, years	14,0±8,2	12,9±9,2	0,521
HLA-B27 positivity	19 (38)	32 (62)	0,04*
Smokers	16 (32)	18 (35)	0,468
BMI, kg/m^2	24,8±6,4	24,8±4,9	0,97
Obesity	10 (20)	8 (15)	0,774
Total cholesterol, mmol/L	4,8±1,0	4,8±0,9	0,843
eGFR, ml/min/1.73 m^2	88,4±14,7	86,6±17,8	0,579
Arterial hypertension	18 (36)	14 (27)	0,323
BASDAI, points	4,7±2,2	5,6±2,1	0,038*
BASDAI >4	25 (52)	38 (81)	0,003*
ASDAS-CRP, points	3,2±1,0	3,8±1,0	0,004*
ASDAS-СРБ ³2,1/ ASDAS-CRP ³2,1	39 (78)	46 (88)	0,015*
Therapy of axSpA			
NSAIDs	46 (92)	49 (94)	0,713
Glucocorticoids	21 (42)	31 (60)	0,075
DMARs, including:	24 (48)	35 (67)	0,048*
Methotrexate	8 (33)	9 (26)	0,844
Sulfasalazine	6 (25)	22 (62)	0,001*
Methotrexate + sulfasalazine	2 (8)	1 (3)	0,614
Methotrexate/sulfasalazine + bDMARDs	3 (13)	2 (6)	0,675
bDMARDs	5 (21)	1 (3)	0,109

Notes: axSpA — axial spondyloarthritis, HLA-B27 — human leukocyte antigen-B27, BMI — body mass index, eGFR — estimated glomerular filtration rate, NSAIDs — non-steroidal anti-inflammatory drugs, DMARs — disease-modifying antirheumatic drugs, bDMARDs — biological disease-modifying anti-rheumatic drugs. * — p <0,05

To assess the rigidity of the vascular wall, the oscillography method was used (TensioClinic arteriograph, Tensiomed, Hungary) with the calculation of the aortic augmentation index (Aix-ao), brachial artery augmentation index corrected for heart rate (Aix-br) and pulse wave velocity of the aorta (PWVao), as well as the photoplethysmography method (AngioScan device, AngioScan-Electronics, Russia) with determination of the stiffness index (SI) and reflection index (RI). Intima-media complex thickness (IMCT) of the right and left common carotid artery was assessed by ultrasound examination in B-mode using an Acuson 128 XP/100 device according to the standard technique [14]. Average IMCT was calculated; an increase in TCIM of ≥0.9 mm was regarded as a marker of subclinical atherosclerosis.

Statistical analysis was performed using SPSS 26.0 software (IBM SPSS Statistics, USA). Checking the distribution for compliance with the normal law was carried out using the analysis of histograms and the Kolmogorov — Smirnov test with Lilliefors correction; the distribution was considered normal at p> 0.05. To describe normally distributed quantitative parameters, the mean value and mean standard deviation (M±SD) were used; to describe the distribution of parameters different from the normal distribution, the median, upper and lower quartiles were defined (Me [Q1-Q3]). To assess the difference in quantitative parameters in two independent groups, Student's t-test was used with normal distribution of data; the Mann — Whitney test was used for distribution other than normal. The Kruskal-Wallis test was used to compare three or more groups. To assess the differences in categorical variables, the Pearson χ^2 test or Fisher's exact test was used. The correlation of two normally distributed quantitative parameters was studied using the Pearson method; for distribution other than normal, Spearman's method was used. Differences were considered statistically significant at p <0.05.

This study was approved by the Ethics Committee of the V.I. Razumovsky Saratov State Medical University of the Ministry of Health of Russia.

Results

Decreased hemoglobin level in patients with anemia corresponded to mild anemia in 49 (94%) cases, and to moderate anemia in 3 (6%) cases. Anemia of chronic disease (ACD) was revealed in 15 (29%) patients; 29 (56%) had a combination of ACD and iron deficiency anemia (IDA); in 8 (15%) patients, isolated IDA was observed. Laboratory and clinical activity of systemic inflammation, according to the obtained values of CRP, ESR, BASDAI and ASDAS-CRP indices, was statistically significantly higher in patients with anemia (Tables 1, 2).

During the analysis of pulse wave properties, no significant differences in vascular wall stiffness indices in axSpA patients with and without anemia were found (Table 3). PWVao values above 10 m/s were registered in 3 (6%) patients without anemia and in 2 (4%) patients with anemia (p=0.675). Mean SI values in patients with normal and reduced hemoglobin exceeded the reference range, while the percentage of patients with increased SI >8 m/s among axSpA patients with and without anemia was 56% and 60%, respectively (p=0.714) An increase in IMCT^{3}of 0.9 mm was observed in 8 (16%) patients with axSpA without anemia and in 4 (8%) patients with anemia (p=0.312).

According to the results of correlation analysis, statistically significant correlations were obtained between Aix-ao, PWVao, SI, IMCT and the age of patients, between Aix-ao, PWVao and BASDAI clinical activity index.

Table 2. *The main hematological parameters and traditional markers of inflammation in patients with axSpA included in the study*

Parameter	All patients with axSpA (n=102)		p
	Without anemia (n = 50) M±SD / Me [Q1-Q3]	With anemia (n = 52) M±SD / Me [Q1-Q3]	
Red blood cells, 10^{12}/L	4,7±0,3	4,2±0,5	<0,001*
Hemoglobin, g/L	138 [134-149]	116 [107-120]	<0,001*
Hematocrit, %	42,0±3,6	34,9±2,5	<0,001*
Mean corpuscular volume (MCV), fL	89 [87-95]	84 [78-89]	<0,001*
Mean cellular haemoglobin content (MCH), pg	30,5 [29,1-31,9]	27,5 [25,2-30,1]	<0,001*
Red cell distribution width (RDW), %	13,5 [12,6-14,2]	15,1 [13,6-17,2]	<0,001*
Platelets, 10^9/L	249 [218-301]	297 [250-371]	0,001*
ESR, mm/h	10 [6-15]	17 [12-28]	<0,001*
CRP, mg/L	9,5 [3,8-15,3]	16,9 [6,7-37,7]	0,003*

Notes: ESR — erythrocyte sedimentation rate, CRP — C-reactive protein. * — p <0,05

Table 3. The main indicators of arterial stiffness and IMT in patients with axSpA with and without anemic syndrome

Parameter	All patients with axSpA (n=102)		p
	Without anemia (n = 50) M±SD	With anemia (n = 52) M±SD	
Oscillography			
SBP, mm Hg	130,3±16,0	129,1±19,2	0,729
DBP, mm Hg	75,4±12,2	75,0±14,1	0,896
MAP mm Hg	93,7±13,0	93,1±15,4	0,837
PP, mm Hg	54,9±8,3	54,0±9,3	0,608
HR, beat/min	72,1±10,7	73,4±11,3	0,564
SBPao, mm Hg	122,8±19,9	119,9±20,5	0,471
	17,3±10,6	19,1±13,7	0,455
Aix-br, %	-40,2±20,9	-36,6±27,1	0,455
PWVao, m/sec	7,4±1,4	7,4±1,5	0,99
Photoplethysmography			
SI, m/sec	8,8±2,0	8,2±1,7	0,183
RI, %	60,6±15,0	54,3±16,7	0,069
Carotid ultrasound			
IMT, cm	0,73±0,16	0,70±0,13	0,421

Notes: SBP — systolic blood pressure, DBP — diastolic blood pressure, MAP — mean arterial pressure, PP — pulse pressure; HR — heart rate, SBPao — central systolic blood pressure, Aix-ao — aortic augmentation index, Aix-br — HR-corrected brachial augmentation index, PWVao — aortic pulse wave velocity, SI — stiffness index, RI — reflection index, IMT — intima-media thickness

Table 4. Relationships between Aix-ao, PWVao, SI, TCIM and traditional cardiovascular risk factors, axSpA activity indices and laboratory parameters

Parameter	Aix-ao		PWVao		SI		IMT	
	r	p	r	p	r	p	r	p
Age	**0,488**	**<0,001***	**0,516**	**<0,001***	**0,289**	**0,007***	**0,461**	**<0,001***
axSpA duration	**0,199**	**0,045***	0,156	0,116	**0,336**	**0,002***	0,167	0,135
SBP	0,032	0,752	**0,355**	**<0,001***	0,192	0,077	0,219	0,05
DBP	**0,305**	**0,002***	**0,434**	**<0,001***	**0,318**	**0,003***	0,211	0,059
BASDAI	**0,243**	**0,018***	**0,253**	**0,013***	0,003	0,981	0,179	0,117
ASDAS-CRP	0,075	0,467	0,131	0,204	0,074	0,51	0,069	0,548
Hemoglobin	-0,131	0,189	0,024	0,815	0,095	0,386	0,158	0,159
Hematocrit	-0,083	0,437	0,17	0,111	0,125	0,289	0,125	0,3
ESR	0,034	0,736	0,129	0,197	0,026	0,811	-0,199	0,077
CRP	-0,022	0,834	0,131	0,201	0,103	0,358	-0,106	0,36

Notes: Aix-ao — aortic augmentation index, PWVao — aortic pulse wave velocity, SI — stiffness index, IMT — intima-media thickness, SBP — systolic blood pressure, DBP — diastolic blood pressure, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein. * — p <0,05

No correlations between the parameters of vascular wall stiffness, IMCT and conventional laboratory markers of inflammation, and hemoglobin level were established (Table 4). Correlations were found between PWVao and Aix-ao (r=0.442, p <0.001), SI (r=0.273, p=0.011) and IMCT (r=0.236, p=0.034).

Discussion

As far as we know, this study is the first one to attempt to assess the correlation between hemoglobin level and vascular wall stiffness, subclinical atherosclerosis in patients with axSpA. The determination of IMCT and arterial stiffness parameters (their increased values are associated with the subsequent development of adverse cardiovascular events) is an important tool for stratification of cardiovascular risk and selection of adequate disease-modifying drugs in patients with axSpA. Data accumulated to date clearly demonstrate the high incidence of subclinical atherosclerosis among patients with axSpA. According to the meta-analysis performed by Yuan Y. et al. [15], IMCT in patients with ankylosing spondylitis (AS) was statistically significantly higher than in healthy controls (standardized mean difference

[95% confidence interval (CI)] = 0.725 [0.443–1.008], p <0.001). According to a systematic review and meta-analysis performed by Bai R. et al.[11] with a total of 2,882 subjects (1,535 patients with AS and 1,347 healthy individuals), a statistically significant increase in PWVao was revealed in patients with AS compared to the control group (weighted average difference [95% CI] = 0.910 [0.464-1.356], p <0.001). IMCT values and vascular wall stiffness parameters obtained during our study in patients with axSpA are consistent with literature data.

However, the objective of this study was to assess the possible correlation between hemoglobin level and the presence of subclinical atherosclerosis in patients with axSpA. At the moment, the role of anemia in the processes of vascular wall remodeling remains a subject of discussion, and study results are sometimes contradictory. On the one hand, it is known that IDA and ACD are associated with the development of oxidative stress [16], and persistent systemic inflammation makes an independent contribution to the dysfunction of antioxidant systems with underlying overproduction of reactive oxygen species [17]. The combined effect of these factors leads to impaired endothelial function, which is a key pathological pattern underlying the development of atherosclerosis [18]. In a study performed by Schwarz C. et al., a negative correlation was demonstrated between hemoglobin level and PWVao (r=-0.31, p=0.01) in patients on hemodialysis [19]. At the same time, H. Hsu et al. [20] reported a positive correlation between hemoglobin concentration and arterial stiffness in dialysis patients, while hemoglobin levels >109 g/l were significantly associated with increased PWVao >10 m/s. A survey of 807 male subjects with and without cardiovascular diseases by Kishimoto S. et al. [21] showed that both a decrease and an increase in hemoglobin, hematocrit and the number of RBC were associated with impaired endothelial function, increased brachial-ankle pulse wave velocity (baPWV) and IMCT of brachial artery. According to Kishimoto S. et al., hematocrit 42.0–49.4%, hemoglobin 147–168 g/l and RBC 4.82–5.24×10⁶/μl are optimal

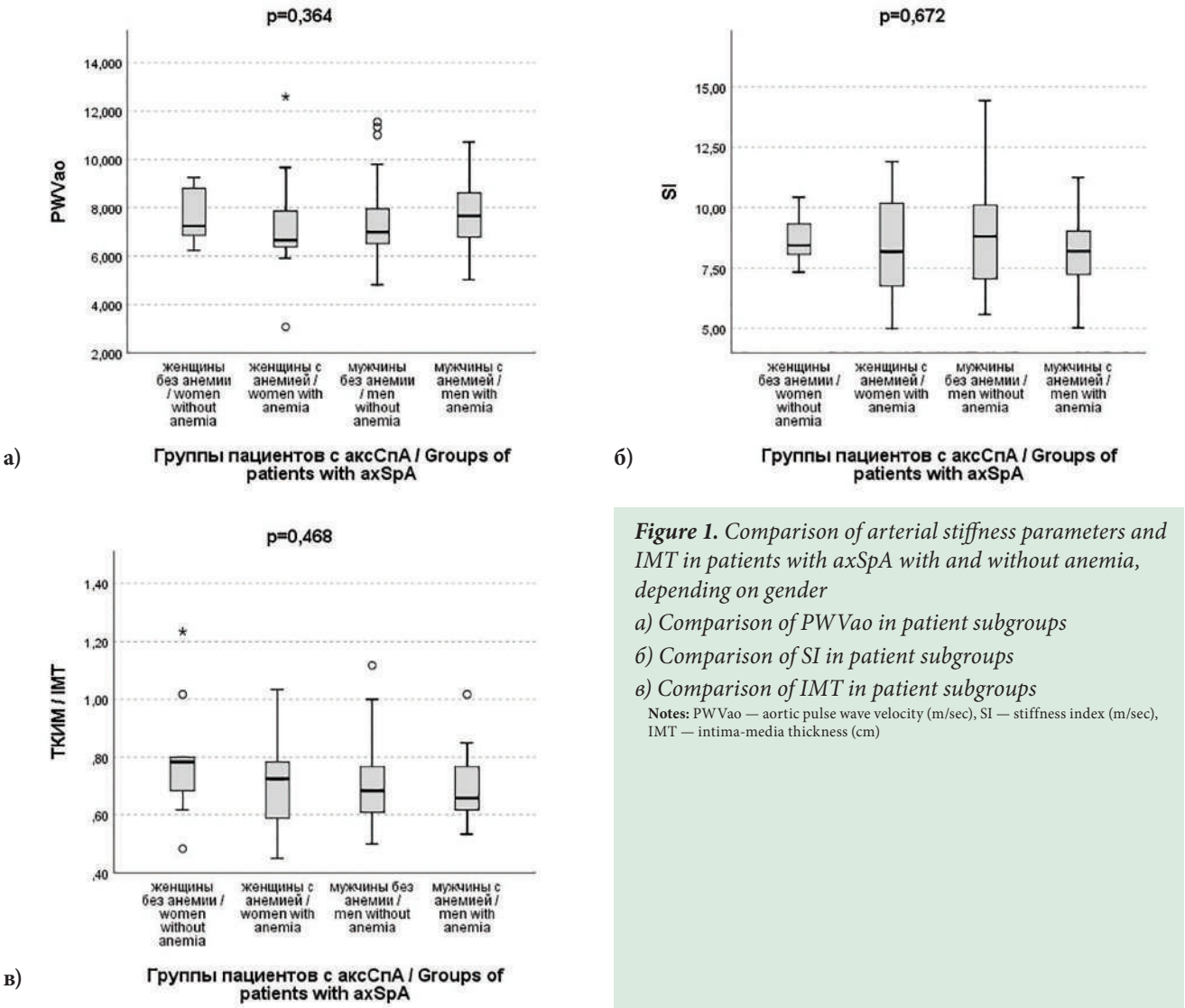

Figure 1. *Comparison of arterial stiffness parameters and IMT in patients with axSpA with and without anemia, depending on gender*

а) Comparison of PWVao in patient subgroups

б) Comparison of SI in patient subgroups

в) Comparison of IMT in patient subgroups

Notes: PWVao — aortic pulse wave velocity (m/sec), SI — stiffness index (m/sec), IMT — intima-media thickness (cm)

target levels for adequate endothelial function and state of vascular wall. A population-based Gutenberg Health Study (GHS) [22] with a total of 13,724 subjects demonstrated an independent association of higher hematocrit values with increased SI in patients of both genders; in men, hematocrit was an independent predictor of increased SI, even in the absence of cardiovascular factors. A large Chinese study by Sun P. et al. demonstrated similar results [23]: there was a significant increase in baPWV and Aix-br with increased concentration of hemoglobin and number of RBC. A group of Japanese researchers [24] obtained data that indicate the potentially protective role of a small decrease in hemoglobin levels — in female patients with mild anemia, baPWV values were lower than in females with normal and increased hemoglobin levels.

Interestingly, despite the significantly higher inflammatory activity of axSpA in patients with anemia (Tables 1, 2), this study did not reveal significant differences between the studied markers of vascular wall remodeling in comparison with patients without anemia. The negative effect of highly active systemic inflammation registered in patients with anemia was probably partially offset by the relative improvement in blood rheological properties due to decreased blood viscosity, as well as increased nitric oxide production induced by hypoxia [25]. Of course, further study of markers of endothelial dysfunction in patients with axSpA and anemia is necessary to determine correlation with parameters of arterial stiffness and subclinical atherosclerosis. It is also worth noting that the percentage of female patients in our study among patients with anemia was higher compared to patients without anemia, 50% and 20%, respectively (p=0.002). However, during the analysis of subgroups by gender, no significant differences between the parameters of arterial stiffness and IMCT in men and women depending on the presence of anemia were found (Fig. 1).

Conclusion

This study could not confirm a correlation between anemia and vascular wall stiffness, IMCT in patients with axSpA. It is possible that the decrease in hemoglobin did not lead to a further increase in the rigidity of the vascular wall due to the potential protective effect of anemia via well-known pathophysiological patterns — decreased blood viscosity and induction of nitric oxide synthesis, which is an endogenous vasodilator and has a strong antiatherogenic effect. Further study of the correlation between hemoglobin levels and markers of endothelial dysfunction in patients with inflammatory diseases of the spine is required.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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