

THE RISK OF CARDIOVASCULAR EVENTS IN PATIENTS WITH ANKYLOSING SPONDYLITIS AFTER COVID-19

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Abstract

Ankylosing spondylitis is a chronic systemic inflammatory disease with predominant damage to the axial skeleton (sacroiliac, intervertebral, costovertebral joints). Systemic inflammatory diseases are characterized by a high incidence of adverse cardiovascular events (fatal and non-fatal myocardial infarction, stroke, unstable angina, sudden coronary death, etc.). This, as a rule, cannot be explained from the standpoint of classical risk factors: hypercholesterolemia, smoking, arterial hypertension, family history, etc. Thus, in rheumatoid arthritis, the frequency of adverse cardiovascular events is 3.96 times higher than in the general population.

Keywords: ankylosing spondylitis, COVID-19, endothelial dysfunction, flow-mediated dilation.

Introduction

Ankylosing spondylitis is a chronic systemic inflammatory disease with a predominant involvement of the axial skeleton (sacroiliac, intervertebral, vertebral joints). Systemic inflammatory diseases are characterized by a high incidence of adverse cardiovascular events (fatal and non-fatal myocardial infarction, stroke, unstable angina, sudden coronary death, etc.). As a rule, this cannot be explained from the standpoint of classical risk factors:

hypercholesterolemia, smoking, hypertension, burdened heredity, etc. Thus, in rheumatoid arthritis, the incidence of adverse cardiovascular events is 3.96 times higher than in the general population.

Adjustment for classical risk factors only slightly changes this risk (indicator), which remains equal to 3.17 [1,3]. A similar pattern is observed in systemic lupus erythematosus. The risk of coronary heart disease (CHD), calculated taking into account traditional cardiovascular risk factors, in these cases is 8-10 times higher than the average population [2], and the risk of myocardial infarction in patients with this disease aged 35 to 44 years is 50 times higher than expected [5]. For ankylosing spondylitis, the prevalence of cardiovascular pathology is very limited, but the results of the existing studies confirm the above trend. The largest work to date regarding the causes of death of patients with ankylosing spondylitis included 836 patients. It has been shown that the risk of fatal cerebrovascular events in this disease is 2 times higher than the similar population indicator, and for other cardiovascular events the risk is 1.4 times higher [7]. A later study showed that mortality among patients with ankylosing spondylitis is 1.5 times higher than the population level, and the main causes of death are secondary amyloidosis and cardiovascular pathology [6]. These data indicate the presence of factors in patients with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis that lead to the development and progression of cardiovascular pathology regardless of classical risk factors.

Systemic inflammation is the main candidate for this role [6]. Inflammatory mediators (C-reactive protein, TNF- α , interleukins-1, -6, and -18) are able to activate endothelial cells. As a result, production of adhesion molecules, selectins, tissue factor, monocytic colony stimulating factor increases with simultaneous reduction of nitric oxide (NO) production [7, 8]. This condition, characterized as endothelial dysfunction, is the initial stage of the atherosclerotic process [9]. At later stages, the same mechanisms are involved in the destabilization of atherosclerotic plaque with the development of acute coronary syndrome, myocardial infarction, transient ischemic attack and stroke [10-12].

Endothelial dysfunction is considered as the main, though not the only, mechanism mediating the influence of systemic inflammation on the development of cardiovascular pathology. Inflammatory mediators are able to suppress insulin-mediated glucose utilization by skeletal muscle [13], stimulate lipolysis in peripheral tissues, as well as synthesis of fatty acids and triglycerides in the liver. In addition, they suppress the activity of endothelial lipoprotein lipase, which is responsible for the catabolism of triglyceride-rich lipoproteins. This leads to the formation of a pro-atherogenic lipid profile, which was noted

by researchers in both rheumatoid arthritis and ankylosing spondylitis [10,11]. Another factor capable of increasing cardiovascular risk in systemic diseases is increased prothrombotic potential. Rheumatoid arthritis is characterized by thrombocytosis [9], increased fibrinogen (acute phase index, the formation of which in the liver is stimulated by interleukin-6), Willebrand factor (procoagulant factor and endothelial injury marker), D-dimer, plasminogen activator inhibitor [13], which correlates with systemic inflammation activity. In ankylosing spondylitis, elevated levels of fibrinogen, D-dimer and Willebrand factor are also detected [10].

Thus, the assessment of classical risk factors alone seems insufficient to determine cardiovascular risk in patients with systemic diseases in general and ankylosing spondylitis in particular. However, to date, there is practically no work on the comprehensive assessment of classical and new cardiovascular risk factors in ankylosing spondylitis. This makes the interpretation of cardiovascular risk stratification results using conventional methods in this category of patients uncertain. The purpose of the work is to study the role of systemic inflammation and endothelial dysfunction as factors contributing to an increase in cardiovascular risk in patients with ankylosing spondylitis.

Materials and methods. The study involved 100 patients diagnosed with ankylosing spondyloarthritis who have undergone COVID-19. The average duration of AS disease was $8,3 \pm 0,6$ years. The average age was $55,2 \pm 1,3$ years, 66 men and 34 women, the control group was 40 healthy persons, the average age of which was $33,5 \pm 1,6$ years, 30 men and 10 women. All patients underwent general clinical, laboratory-instrumental diagnostic methods, assessment of disease activity according to the VAS scale and BASDAI, BASMI, ASDAS indices to establish the diagnosis of AS.

All patients were screened for hypertension (AH) and classic cardiovascular risk factors: smoking, hyper- and dyslipidemia (total cholesterol, high-density lipoprotein, triglyceride levels were studied with calculation of low-density lipoprotein levels using the formula of W.T. Friedewald et al. [10] and atherogenicity index), excess body weight (with body mass index [BMI] ≥ 25 kg/m²), heredity, diabetes mellitus. The diagnosis of AH was established with three-fold detection of blood pressure above 140 and 90 mm Hg (during hospitalization or according to medical records). For all patients, 10-year coronary risk (risk of CHD) was calculated on the Framingham scale [8]. This scale takes into account sex, age, total cholesterol and high-density lipoprotein levels, blood pressure levels, diabetes presence, and smoking status. In addition, a 10-year fatal risk (risk of death from CHD, atherosclerosis of the cerebral and peripheral arteries) was calculated according to the SCORE (Systematic Coronary Risk Evaluation) scale [11]. This scale includes gender, age, OX,

systolic blood pressure, and smoking status. The risk of fatal complications on the SCORE scale is considered low if it is < 5%; high - with a value ranging from 5% to 10%, and very high if it exceeds 10%. "New" or additional cardiovascular risk factors currently include markers of systemic inflammation, indicators of the hemostasis system, markers of endothelial damage and dysfunction, and a number of others [12]. We studied the levels of C-reactive protein, fibrinogen, platelets in peripheral blood, Willebrand factor activity, antithrombin III activity, and total plasma fibrinolytic activity.

To determine endothelin-1 as the main marker of endothelial dysfunction, the patients' venous blood serum was taken and examined by ELISA. ELISA KIT for ENDOTHELIN-1 (USA) was used as a reagent. To assess the functional state of the endothelium, a dopplerographic examination of the brachial artery was performed on the Acuson 128 XP/10 complex equipped with a 7 MHz linear sensor in samples with reactive hyperemia (endothelium-dependent stimulus) and nitroglycerin (endothelium-independent stimulus). Prior to the functional tests, the initial diameter of the brachial artery and the initial blood flow rate were determined. Occlusion of the artery was carried out using a pneumatic cuff applied to the shoulder proximally to the located area. The cuff was pressurized to 30 mmHg above systolic blood pressure. The lack of blood flow was monitored Doppler-graphically; duration of occlusion - 5 min. After the termination of occlusion, reactive hyperemia is observed in the localized section of the brachial artery, which leads to an increase in shear stress on the endothelium, deformation of endotheliocytes, activation of NO synthase, stimulated NO synthesis and, as a result, vasodilation. The brachial artery diameter and blood flow rate were determined every 15 seconds for the first minute after the occlusion was stopped. Endothelium-dependent vasodilation (ESRD) was calculated using the formula $ESVD = (d_{60} - d_0) \times 100 \% / d_0$, where d_{60} is the diameter of the brachial artery 60 seconds after the resumption of blood flow, d_0 is the original diameter of the brachial artery. A normal reaction of the brachial artery to reactive hyperemia is conventionally considered an increase in its diameter by 10% from the original [7]. 10-15 minutes after the study with reactive hyperemia, after restoring the diameter of the brachial artery and Doppler blood flow to baseline values, the patient received sublingual nitroglycerin at a dose of 500 µg. For the next 5 minutes, the diameter of the brachial artery was determined every minute. Endothelium-independent vasodilation (ENVD) with nitroglycerin was calculated using the formula: $ENVD = (d_5 - d_0) \times 100 \% / d_0$, where d_5 is the diameter of the brachial artery 5 minutes after nitroglycerin, d_0 is the initial diameter of the brachial artery. The control group includes 30 practically healthy people (28 men and 2 women) aged $36,2 \pm 10,3$ years (which is comparable to the average age of patients in the main group) who do not have AH, diabetes mellitus, CHD and its equivalents.

Among the controls, 19 (63.3%) were smokers, which is also comparable to the ankylosing spondylitis group.

Statistical processing of the results determined the nature of the data distribution using the graphical method and the Kolmogorov-Smirnov test. The distribution pattern was considered normal at $p > 0.05$. Descriptive statistics methods were used when comparing two groups with the normal nature of the data distribution, the t-test for independent groupings was used, and non-parametric statistical methods were used for the nature of the distribution, the Mann-Whitney test and the Wald-Wolfowitz test.

Results and discussion. 31 (31%) patients had 1 and 2 grades of arterial hypertension (AH). Adequate antihypertensive therapy among them was received by 15 patients (48.3%). The detected incidence of AH in patients with ankylosing spondylitis is close to the prevalence of AH in the general population (26.4%). Screening of classical cardiovascular risk factors yielded the results shown in Table 1.

Table 1. Incidence of classical risk factors in observed subjects

Risk factor	Frequency(%)
Smoking	70
Hypercholesterolemia (total cholesterol ≥ 5 mmol/L)	13
Low HDL (< 1 mmol/L for men, < 1.2 mmol/L for women)	61
High LDL ($\geq 3,0$ mmol/L)	22
Hypertriglyceridemia (triglyceride level ≥ 1.7 mmol/L)	13
Overweight /obesity(BMI ≥ 25 kg/m ²)	29
Family history of early heart disease	24
Diabetes	0

The high incidence of smoking among patients with ankylosing spondylitis can be explained by the predominance of males, with a smoking index of 240 and a smoking history of 14 in unit-years. When analyzing lipid metabolism disorders, a high frequency of reduced levels of high-density lipoproteins (61%) with a relatively low (13%) frequency of

hypercholesterolemia detection is noteworthy. Lipid profiles of patients and controls are presented in Table 2.

In patients with ankylosing spondylitis, total cholesterol is significantly lower than in the control group. Low-density lipoprotein and triglyceride levels were found to be comparable to those of healthy individuals. At the same time, patients with ankylosing spondylitis showed a significant decrease in the level of high-density antiatherogenic lipoproteins. This seems to be the reason for the significantly higher value of the atherogenicity index compared to the control group. Thus, the lipid profile in patients with ankylosing spondylitis (AS) can be characterized as proatherogenic, which is not associated with hyperlipidemia, but with low levels of high-density lipoproteins. The mean BMI was $23,4 \pm 4,6$ kg/m², the majority of patients (64%) had normal body weight (BMI = 18,5-24,9 kg/m²), 7% of patients had a body weight deficit (IMT25 kg/m²), including 11% - obesity (BMI > 30 kg/m²).

Table 2. Lipid spectrum indications in observed groups

Indication	Main group(n=100)	Control group (n=40)
HDL (mg/dL, ≥ 60)	51,9 \pm 2,8	69,2 \pm 3,7
LDL (mg/dL, < 100)	138,4 \pm 9,1	79,2 \pm 3,4
Triglycerides (mg/dL, ≤ 150)	132,4 \pm 3,9	125,7 \pm 1,9
Cholesterole (мг/дл, <200)	219,6 \pm 4,7	175,2 \pm 8,6
Atherogenicity index	4,13 \pm 1,11	2,65 \pm 0,77

The ten-year risk of fatal cardiovascular events on the SCORE scale in examined patients was 1.0 %, which may be considered a low level. At the same time, only 5 patients had a 10-year fatal risk of 5% or more (from 5 to 7%). Thus, the assessment of only classical risk factors allows us to conclude that in patients with ankylosing spondylitis, the risk of CHD, as well as the risk of fatal cardiovascular events, is low and, at least, comparable to the population indicator. This contradicts the above data on the increased incidence of adverse cardiovascular events in patients with systemic diseases. Therefore, analysis of additional (or "new") cardiovascular risk factors is of particular importance. The level of C-reactive protein exceeding 10 mg/L, considered in recent years as one of the main cardiovascular risk factors, was noted in 54% of patients. This is quite natural, given the inflammatory nature of ankylosing spondylitis. Fibrinogen levels in patients with ankylosing spondylitis are also expected to be higher than in controls ($7,2 \pm 2,4$ and $3,5 \pm 0,8$ g/L, respectively, $p < 0.05$). The

fibrinolytic activity of plasma, on the contrary, in ankylosing spondylitis was significantly lower: the lysis time of the euglobulin clot in patients was 11.5 [8.0; 19.0] minutes, and in healthy individuals - 7.0 [5.5; 7,5] ($p < 0,001$). The association between inflammation activity and changes in the hemostasis system is evidenced by a significant correlation of C-reactive protein level with fibrinogen level (Spearman $\rho = 0.492$, $p < 0.001$).

Thus, in patients with ankylosing spondylitis, an increase in prothrombogenic potential is clearly associated with the activity of systemic inflammation. These changes contribute to an increased risk of thrombosis and related adverse cardiovascular events. The results presented in Table 3 were obtained during the study of the functional state of the endothelium.

There were no significant differences in the level of ESD between the groups, however, the proportion of patients with reduced ESD ($< 10\%$) turned out to be significantly larger in the group of patients with ankylosing spondylitis (47% and 18%, respectively, $p < 0.01$). The ENVD reflecting the vascular wall response to exogenous nitrate administration, on the contrary, was significantly greater in patients with ankylosing spondylitis. We believe that increased vascular wall reactivity in response to nitroglycerin in patients with ankylosing spondylitis indirectly suggests endogenous nitric oxide (NO) deficiency. We did not find significant correlations between the levels of ESRD and ENVD with acute phase indicators and individual cardiovascular risk factors. However, ESRD was inversely dependent on the length of ankylosing spondylitis ($r = -0.236$, $p < 0.05$). Figure 1 shows the ultrasound dopplerography of brachial artery with following decrease of FMD, PI and RI.

Table 3. Comparative parameters of the functional state of the endothelium in patients of main and control groups

Indication	Main group (n=100)	Control group (n=40)	P value
Endothelin-1(pg/ml)	243,4±9,1	48,1±7,4	<0.001
FMD(%)	7,3±1,7	8,9±1,6	0.007
Carotid artery wall thickness (mm)	0,52±0,1	0,46±0,1	0.003

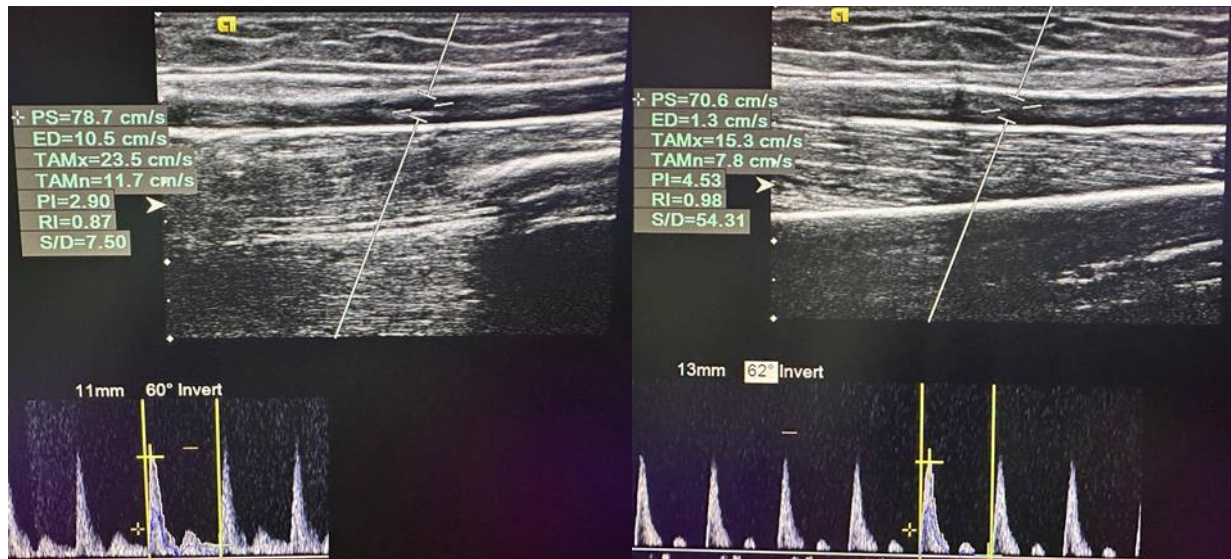


Figure 1. Decreased FMD, increased PI, and RI of brachial artery at 60 seconds after compression test in AC patients undergoing COVID-19

The lack of connection between the indicators of the functional state of the endothelium and markers of the activity of systemic inflammation is, in our opinion, evidence that the main importance in the development of endothelial dysfunction is not so much the current activity of systemic inflammation as the duration of its existence. An indirect confirmation of this is the inverse relationship between ESRD and the duration of ankylosing spondylitis. The low correlation coefficient is explained by the fact that disease duration is not synonymous with the duration of active inflammation. Ankylosing spondylitis can occur with persistent inactive inflammation, as well as in waves, when periods of improvement are replaced by periods of exacerbation lasting from several weeks to several months and years.

Thus, in patients with ankylosing spondylitis, there are signs of endothelial damage (increased levels of Willebrand factor and CEC) and its dysfunction (reduced ESRD is observed in 47% of patients, and ENVD in response to nitroglycerin exceeds not only ESVD, but also ENVD in healthy persons).

Endothelial dysfunction is currently considered as a serious independent predictor of adverse cardiovascular events. In the study by F. Perticone et al. [9] demonstrated a clear inverse relationship between the level of brachial artery ESRD and the incidence of adverse cardiovascular events. These data were obtained during follow-up (an average of 31.5 months) for patients with AH who did not have clinical signs of coronary or peripheral atherosclerosis at the time of inclusion in the study. Similar data were obtained by M.G. Modena et al. [10], according to which reduced ESRD was found to be a predictor of adverse cardiovascular events during a 5-year follow-up period for patients with newly

diagnosed AG. These data suggest that endothelial dysfunction is one of the factors responsible for increasing cardiovascular risk in ankylosing spondylitis.

Conclusions.

The risk of CHD and fatal cardiovascular events in patients with ankylosing spondylitis, calculated taking into account only classical risk factors, is close to general population. The results of the analysis of additional risk factors indicate the presence in patients with ankylosing spondylitis of signs of damage, endothelial dysfunction and increased prothrombogenic potential, directly related to the activity of systemic inflammation. We assume that it is these factors that are responsible for the high risk of cardiovascular events in ankylosing spondylitis and, therefore, should be taken into account when assessing it. Of particular clinical importance is the study of ESVD, which at an early stage makes it possible to identify patients who have a high risk of developing adverse cardiovascular events.

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