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Research Article

PECULIARITIES OF THE DEVELOPMENT OF ISCHAEMIC AND NON-ISCHAEMIC HEART DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS (LITERATURE REVIEW)

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Saidova M.M.
Bukhara State Medical Institute, Uzbekistan

ABSTRACT

The paper presents data on heart damage in patients with rheumatoid arthritis (RA), peculiarities of ischemic and non-ischemic heart disease development with a significant increase in the risk of adverse cardiovascular events. Patients with RA are characterised by an increased risk of myocardial infarction, heart failure, rhythm disturbances, sudden cardiac death and total cardiovascular death. The possibility of fairly rapid development of myocardial dysfunction in RA patients since the manifestation of the disease, the development and progression of coronary atherosclerosis is emphasized, and when RA patients develop coronary artery lesions, the worse survival rate after suffered myocardial infarction is established.

The evidence suggests that rheumatoid arthritis is a significant contributor to cardiovascular morbidity and mortality.

KEYWORDS

Rheumatoid arthritis, heart, myocardium, cardiovascular morbidity and mortality.

INTRODUCTION

Heart disease in rheumatoid arthritis patients - how urgent is this problem today? Do the detected abnormalities have clinical relevance? Let's start the discussion of these questions with the currently established facts and try to clarify the mechanisms of the changes occurring in the heart.

Rheumatoid arthritis (RA) is an autoimmune joint disease that affects 0.5-2.0% of the world's population. In RA, the pathological process involves almost all joints with the development of stiffness, pain, joint structure and function disorders, up to ankylosis. RA is a systemic process that affects not only the joints, but also various internal organs, including the heart. Until

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recently, it was thought that heart disease in RA was clinically insignificant, but in recent years it has been found that patients with RA have a 7-10 year life expectancy, and the risk of coronary disease or myocardial infarction is comparable to that of diabetes mellitus. Patients with RA have an approximately 50% higher risk of cardiovascular events and cardiovascular death. The magnitude of these risks varies from study to study, depending on the cohort of patients included, the nature and efficacy of the therapy, and the time of follow-up. There is evidence of a pooled relative risk value of 1.68 for myocardial infarction and 1.87 for congestive heart failure, and in another study patients with RA had an increased risk of myocardial infarction with an odds ratio (OR) of 2.50 (95% CI; 0.77-8.14), a 60% higher risk of death from cardiovascular disease (CVD) compared to the general population. Thus, we can conclude that RA itself is a risk factor for cardiovascular disease and the development of cardiovascular complications, and that heart damage in patients with RA is clinically significant.What are the main pathways of heart damage in RA patients? The first pathway is coronary artery damage with the formation of coronary artery disease. Rupture of atherosclerotic plaques can cause thrombus formation, which can locally block the coronary blood vessels and lead to acute coronary syndrome. Insufficient oxygen supply to the myocardium can lead to cardiomyocyte dysfunction, which determines the decreased contractile function of the heart muscle. Coronary artery damage can manifest itself as angina pectoris, leading to cardiomyopathy or arrhythmia. In the acute form, complete occlusion of the major arteries can lead to myocardial infarction and sudden cardiac death. Another pathway of heart damage is the development of non-ischaemic heart disease with changes in the cellular composition and structure of the heart muscle. Cardiomyopathy is the most common type of non-ischaemic heart disease, in which hypertrophy of the ventricular myocardium develops and the myocardium itself becomes stiff. Most patients with RA do not present with clinical symptoms characteristic of coronary artery and myocardial damage for many years, especially against a background of joint pain, stiffness, and restricted physical activity, which seems to be the basis for the opinion that the heart is clinically insignificant. However, modern diagnostic capabilities make it possible to detect subclinical and asymptomatic changes in the heart at the earliest stages of RA, and provide an accurate picture of the structure and function of the cardiovascular system. For example, the results of cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET-CT) in patients with RA without a diagnosis of cardiovascular disease indicate that almost 50% of patients already have signs of myocardial fibrosis or inflammation. Changes in the myocardium cause detectable increased left ventricular myocardial mass in patients with RA without arterial hypertension or other CVD, and myocardial hypertrophy may at some stage be accompanied by a reduction in contractile function. Notably, decreased left ventricular systolic and diastolic function is found in 50% of patients with RA without clinical signs of heart failure. In patients without clinically significant cardiac damage, deterioration of left ventricular systolic function, as assessed by left ventricular myocardial deformation as measured by tracing cardiac magnetic resonance characteristics, has been found. The formation of concentric left ventricular myocardial remodelling in patients with RA even before clinical manifestations of cardiovascular disease and in the absence of common cardiovascular risk factors is an important finding. In a study of myocardial deformation during ventricular contraction and relaxation using tracking echocardiography (STE), the longitudinal structure of the left and right ventricular wall at the systolic peak was found to be significantly worse in patients with

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preserved diastolic function. This result was maintained after adjusting for age, gender, blood pressure, BMI and heart rate, after comparing patients with controls.

Subclinical changes in coronary microcirculation were also detected in RA patients. Thus, by measuring myocardial flow reserve, cardiac microvascular dysfunction was found in one third of RA patients without clinical cardiovascular manifestations. In the absence of clinical manifestations of coronary artery disease, patients with RA have higher prevalence, extent and severity of all types of coronary plaques as measured by CT angiography. At the same time, patients with RA are twice as likely to develop episodes of 'silent' (unrecognised) myocardial infarction. These subclinical changes in the myocardium and coronary arteries are the cause of serious ischaemic and non-ischaemic complications. Coronary artery disease is an important cause of cardiovascular death in patients with RA.

Patients with RA have twice the risk of sudden cardiac death, and they are less likely to have clinical manifestations of angina pectoris. In the general population, sudden cardiac death is usually caused by fatal arrhythmias that result from electrophysiological abnormalities in the heart. Patients with early arthritis do not have a higher incidence of prolonged QTc interval than those in the population without arthritis, but proarrhythmic QTc prolongation progresses over time if the process continues. The main pathophysiological mechanism underlying QTc prolongation is systemic inflammation, acting both indirectly by accelerating cardiovascular disease and directly by affecting cardiac electrophysiology. The inflammatory cytokines interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) have been shown to cause profound changes in the expression and function of potassium and calcium channels with increased action potential resulting in prolonged QT interval. Thus, circulating inflammatory cytokine levels have been found to correlate with QTc duration in patients with RA.

QTc length is known to be an independent risk factor for cardiovascular disease. Both moderate (QTc 420-440 msec) and significant QTc prolongation (>440 msec) are prognostic factors for all-cause mortality in healthy middle-aged populations. In patients with RA, an increase in the QTc interval by 50 msec has been found to be associated with a doubling of the risk of overall mortality, an association mediated by CRP levels.

Conduction abnormalities are generally more common in RA patients than rhythm abnormalities. Rhythm disturbances have different pathophysiological mechanisms, of which myocardial inflammation and fibrosis are the most important. Inflammation and oxidative stress lead to cardiomyocyte necrosis followed by electrical and structural remodelling. Chronic inflammation leads to autonomic dysfunction, namely hyperactivation of the sympathetic nervous system and decreased parasympathetic function. Arrhythmias mediated by autoantibodies and medications are also common in patients with RA. At the same time it has been established that in RA patients against tocilizumab therapy (antibodies against IL-6 receptor) a rapid (within 3 months) and significant QTc shortening occurs which correlates with reduction of CRP level. A study of a large cohort of women with RA demonstrated that inflammation, as assessed by circulating levels of IL-6, correlated more strongly with fatal than non-fatal cardiovascular events. Atrial fibrosis is considered a common feature of clinical atrial fibrillation (AF) and a sign of arrhythmogenic myocardial structural remodelling.

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The incidence of AF in patients with RA is 40% higher than in the general population, can occur at any time during the course of the disease, may even be the first manifestation of the disease. Although the pathophysiology of AF in RA is complex, systemic inflammation causing increased concentrations of circulating inflammatory proteins, coronary heart disease and heart failure are important factors for the initiation and recurrence of AF in these patients.

Autonomic nervous system (ANS) dysfunction due to the neurotoxic effects of chronic systemic inflammation and drug side effects is found in 60% of patients with RA. However, ANS dysfunction itself is considered a possible pathogenetic cause of cardiac arrhythmias in RA patients. The primary type of ANS deregulation is impaired cardiovascular reflexes and altered heart rate variability indicating decreased cardiac parasympathetic activity and increased cardiac sympathetic activity manifested by atrial ectopic contractions, heart failure, impaired heart rate control and inappropriate atrial tachycardia.

The most common cause of sudden cardiac death in patients with RA is atherosclerotic coronary artery disease leading to acute coronary syndrome and ventricular tachycardia. Although the underlying mechanisms underlying the proarrhythmogenic substrate in RA are complex, the leading role also appears to be that of chronic systemic inflammatory activation, contributing to arrhythmias both indirectly by accelerating the development of coronary heart disease and congestive heart failure, and directly by affecting the electrophysiology of the heart. There is now evidence that inflammatory cytokines, mainly TNF-α, IL-1 and IL-6, can modulate the expression and function of ion channels, directly affecting cardiomyocytes. There is now new evidence for the role and significance of anti-citrulline antibodies in heart disease. Anti-citruelike antibodies are a key specific feature of RA, they are relatively specific and appear in the preclinical phase of the disease. Today, evidence of the role and significance of the autoimmune process in heart damage in RA can be seen in the association between high levels of anti-citrullinated antibodies targeting cit vimentin and myocardial cit-fibrinogen protein or peptides, and a higher mean left ventricular myocardial mass index value. Citrullination of vimentin, an intermediate filament component of mesenchymal cells, leads to collapse of the filament network, while citrullination of myosin and tropomyosin alters their assembly and contractility patterns. These findings may to some extent explain the detectable early myocardial changes in patients with RA even before the development of cardiovascular disease, as the autoimmune process begins long before the clinical manifestation of joint damage.

In contrast to the well described contribution of systemic inflammation to the early development and progression of atherosclerosis in rheumatoid arthritis, its role in the development of non-ischaemic heart disease is less well understood. Active inflammatory processes in the heart can lead to excessive myocardial fibrosis, causing ventricular stiffness, and contribute to systolic and diastolic dysfunction and cardiac arrhythmias. Cardiac MRI and PET-CT data have confirmed the relationship between disease activity and myocardial inflammation and fibrosis. Structural changes in the myocardium observed on cardiac MRI are also correlated with diagnostic markers of systemic inflammation. High disease activity and elevated CRP levels are associated with an increased prevalence of diastolic heart failure. Improved treatment strategies ("treatment to goal") in patients with RA have reduced cardiovascular risk to a certain extent. The planning of new clinical trials on the effectiveness of different

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therapeutic approaches in patients with RA should take into account the effectiveness of therapy not only to reduce disease activity, but also to be effective in protecting the cardiovascular system and reducing the risk of cardiovascular events.

CONCLUSION

Currently, a high incidence of heart damage has been established in rheumatoid arthritis patients: ischemic and non-ischemic heart disease with a significant increase in the risk of adverse cardiovascular events develops. RA patients are characterised by an increased risk of myocardial infarction, heart failure, rhythm disturbances, sudden cardiac death and total cardiovascular death. An important fact is the establishment of rather rapid development of myocardial dysfunction in patients from the moment of RA manifestation, development and progression of atherosclerosis of coronary arteries. At the same time, patients with RA are characterized by a worse survival rate after myocardial infarction, both in the immediate and in the long term.

The presented data allow us to consider rheumatoid arthritis as a disease that contributes significantly to cardiovascular morbidity and mortality, which necessitates a review of the management of patients with rheumatoid arthritis, defining new therapeutic targets and finding successful cardioprotective therapies for patients.

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