A female pattern of ischemic heart disease - a new look at an old problem

Diseases of the circulatory system are the most common cause of death among women. It should be emphasized that this problem is still underestimated in daily practice. As women are less likely to have significant stenosis in coronary angiography than men, they are regarded to be at smaller risk. At the same time, numerous studies prove that the prognosis of women with ischemic heart disease is serious. Therefore, some researchers suggest distinguishing the so-called “female pattern” of ischemic heart disease, characterized by persistent, often atypical chest pain, positive results for noninvasive tests evaluating ischemia and no significant changes in coronary angiography. It is relevant in the diagnosis of women to assess the global risk, taking into consideration such parameters as inflammation indicators, endothelial dysfunction and microvascular reactivity. There is still no data on optimal treatment, but there seems to be a clear benefit from intensive modification and elimination of risk factors, as well as typical pharmacotherapy with angiotensin-converting enzyme inhibitors, beta-blockers and statins.

Introduction

Diseases of the circulatory system are the most common cause of death among women. As the incidences of diabetes, hypertension, obesity, and lipid disorders increase along with the average life expectancy, a growth in the incidence of cardiovascular diseases and the associated significant deterioration in quality of life are expected in the coming decades. According to WHO data, this problem mainly concerns the countries of Central and Eastern Europe, Latin America, Asia and the Middle East. Improvements observed in recent years in the prognosis of patients with ischemic heart disease concern mainly men [6].

Lasting for decades, the era of invasive examinations reinforced in many doctors a belief that the degree of stenosis in the epicardial coronary arteries indicates the severity of ischemic heart disease. Despite the fact that women more often than men demonstrate less severe atherosclerotic changes, or even normal coronaryography results, they are much more likely to report persistent problems. This is a reason for frequent outpatient medical advice and hospitalizations, as well as a cause of difficulties in daily activities and is connected with a significantly decreased quality of life and a worse prognosis [11,9,5,6]. For this reason, some researchers have suggested introducing the term “female pattern” of ischemic heart disease to distinguish it from a typical “male pattern” associated with the presence of critical stenosis in the coronary arteries [7]. Shaw et al. suggest that the term ischemic heart disease (IHD) is more appropriate for women with anginal complaints with no significant changes in coronaryography than coronary heart disease (CHD) or coronary artery disease (CAD). The authors reserve the latter terms for people with critical stenosis in the coronary arteries [12].
"Female pattern" of ischemic heart disease

The definition of typical coronary pain is mainly based on the male population and includes effort-related complaints typical of critical stenosis in the coronary arteries. In women, regardless of whether they report typical or atypical symptoms (pain unrelated to effort, prolonged discomfort that is not relieved by rest) significant changes in coronary anatomy have been found less frequently [9]. The CASS registry carried out in the 1970s showed that women manifest more intensive symptoms than men with a comparable angiographic image and, despite positive results for noninvasive stress tests, more frequently have a normal picture of the coronary arteries [5]. It is estimated that up to 50% of women who undergo coronary angiography, do not have critical stenosis [12]. For many years it was believed that such a result was connected with a good prognosis and low coronary risk. However, as many as half the patients with a "normal" result of coronary angiography still report problems, which makes further hospitalization and often another angiography necessary. It has an adverse effect on patients’ well-being, intensifies health concerns and generates considerable healthcare costs [5,12].

Is it true that women with chest pain, but no significant changes in coronary angiography, can be considered healthy? Data from the American WISE study (Women’s Ischemia Syndrome Evaluation) proved that persistent symptoms of myocardial ischemia significantly increase the risk of coronary events and rates of mortality in the group of women with no significant changes in the epicardial arteries (stenosis 1-49%) compared to asymptomatic women from the general population [3]. The risk of adverse events rose with age (after the age of 62 there were no significant differences between women with no stenosis and those from the general population) and the number of co-existing risk factors [3]. Similar observations have been made by Shaw et al. in their study on acute coronary syndromes [12]. After the analysis of data from almost 460,000 patients, they concluded that significant stenosis in the coronary arteries occurred 50% less frequently in women. According to various reports, 10-25% of women with ST-segment elevation myocardial infarction (STEMI) and 6-10% of men have a "normal" result of coronary angiography [12]. In a Polish population of 1,219 patients with non-ST-segment elevation myocardial infarction (NSTEMI), 18.9% of women and 11% of men manifested no atherosclerotic changes in the coronary arteries displayed in coronary angiography (p = 0.035) [4], whereas multivessel disease affects men and women with equal frequency in both the STEMI and NSTEMI populations [4,9]. Despite the less advanced stages of disease in angiography, women are more prone to progress after myocardial infarction [9,10]. It is partly explained by the older age of women and more risk factors at the moment of infarction, however differences in prognosis are also evident in younger age groups. The reasons for this paradox are not fully understood [6,7].

Pathomechanism

For years, the existence of sex-related differences in the development of atherosclerosis has been postulated. Attention has been paid to the protective effect of endogenous estrogens and different mechanisms for the development of acute coronary syndrome in women. The erosion of atherosclerotic plaques and neointimal hyperplasia is a more often mentioned [2]. The use of new diagnostic methods, both imaging (intravascular ultrasound, magnetic resonance imaging, computed tomography) and biochemical, provides an increasingly better understanding of differences between "female" and "male" patterns of ischemic heart disease. In the face of current studies, it appears that sex differences result from several mechanisms: intense inflammation, abnormal muscle contractile response of the coronary arteries, endothelial dysfunction and endothelium-independent regulation of microcirculation [12,2].

Inflammatory processes play an important role in the pathophysiology of metabolic syndrome and the development of atherosclerotic plaque. At present, we can monitor the severity of inflammation using different markers (interleukins, procalcitonin, fibrinogen, C-reactive protein). The evaluation of the last parameter, especially using high-sensitivity methods (hsCRP), has a fairly well-documented value in coronary risk stratification [2]. In women, CRP values are usually higher than in men. This difference appears in adolescence and it seems that it is associated with an increased incidence of chronic inflammatory diseases such as rheumatoid arthritis, lupus, thyroid diseases, etc. in women. An increased predisposition to the occurrence and maintenance of inflammation, expressed by elevated CRP values, may contribute to slightly different clinical manifestations of ischemic heart disease in women. The inclusion of hsCRP in the group of routinely assessed risk factors may also contribute to better coronary risk estimation in women [12,2].

The correct endothelial function is essential for the regulation of flow through the small vessels. Its injury is one of the important stages in the development of atherosclerosis in both women and men. The factors that cause endothelial dysfunction include hyperglycemia, hyperlipidemia and hypertension. The hypothesis, proposed by some authors, asserts that the interaction of several factors - metabolic, hormonal and gender - plays a relevant role in the pathomechanism of endothelial dysfunction in women - chronic inflammation, loss of the protective effect of estrogens during menopause and the associated increased action of traditional coronary risk factors. An impaired endothelial function, evaluated based on changes in flow through the brachial artery, is a documented risk factor for coronary events in women, whereas its improvement has a beneficial effect on the prognosis [12,2].

It seems that changes that occur at the level of microcirculation seem to be particularly important in the pathomechanism of ischemic heart disease in women. Women are more likely to suffer from various diseases associated with abnormal functioning of the small vessels (migraine headaches or Raynaud syndrome). A link has been found between the degree of retinal arteriolar narrowing and coronary events in women, but not in men [12].

The correct regulation of coronary microcirculation enables, depending on the needs, as much as a fivefold increase in the blood flow through the heart muscle. Impairment of this ability may be the first symptom of ischemic heart disease and may result from both endothelial dysfunction and other mechanisms [12,2]. Data from studies conducted using intravascular ultrasound confirm that women more frequently develop changes in microcirculation, while men develop changes in the epicardial vessels [12].

Disorders of non-endothelial microvascular regulatory mechanisms have been studied less often than endothelial dysfunction. An adenosine-dependent relaxant response of the smooth muscles of arterioles is better recognized. It has been shown that hypercholesterolemia and hypertension can modify its course in a different way in both sexes. In addition, an abnormal reaction may occur both in atherosclerotic and healthy vessels [12,2]. Pepin et al. showed that no improvement in the microvascular flow after the administration of adenosine into the coronary circulation was associated with a higher risk of adverse cardiovascular events in women with no significant stenosis [8].

A different location of the disease - at the periphery of the vessel, can cause other types of symptoms such as poor exercise tolerance - manifested rather as dyspnea and weakness than typical anginal pain and prolonged pain unrelated to effort, induced by strong emotions. Shaw et al. suggest defining these problems as "microvascular angina" [12], while at the Congress of the European Society of Cardiology in 2011, a researcher dealing with this issue, C.N. Merz introduced the term "microvascular coronary dysfunction" (MCD) [1].

Diagnostics and prognosis

No exact guidelines on how the tests should be done and interpreted have been worked out so far. The method of small vessel evaluation used in previously cited studies was invasive and feasible only in specialized centers. It was based on the administration of adenosine and acetylcholine into coronary circulation followed by the assessment of flow using the Doppler method by means of intravascular ultrasound.

Currently existing diagnostic methods are designed to detect critical stenosis in the large coronary arteries, which is a typical symptom of the "male pattern" [12]. The results of noninvasive tests that indicate myocardial ischemia (exercise test, SPECT) with no evidence of coronary angiography are usually defined as "false positives". However, given a different course of ischemic heart disease in women, perhaps this approach should be verified. We should consider such results in the context of the whole clinical picture and weigh further examinations that would help to evaluate microcirculation [6,7,12]. How, then, can we identify...
a “female pattern” of ischemic heart disease using commonly available noninvasive tests.

Exercise ECG testing is one of the most commonly performed tests in the diagnosis of ischemic heart disease. However, interpreting the result is particularly difficult in the female population. This is due, among other things, to women’s lesser physical strength and the consequent inability to do maximum Duke and their ability to achieve maximum heart rate too quickly or excessive hypertensive reaction. The need to interrupt the test too early makes establishing a diagnosis impossible. We also know that female sex hormones may cause changes to the ST segment in the ECG, which is an additional difficulty in the overall assessment of the test. However, there are parameters which have been proved to be highly effective in the assessment of coronary risk in women. They include the ability to perform a total effort of more than 5 METs and the evaluation of changes in the heart rate after finishing physical exercise. Most daily activities require an effort of about 4 METs. The 12-lead Duke Activity Status Index (DASI), was created, which allows an approximate estimation of women’s exercise capacity. In the WISE study, an inability to perform an effort exceeding 4.7 METs was associated with a nearly 4-fold higher risk of death or nonfatal myocardial infarction, while an improvement of exercise capacity by 1 MET reduced the risk of coronary events by 8%. The persistent accelerated heart rate after finishing physical exercise is another adverse prognostic factor. It has been shown that if a difference between maximum heart rate and that measured in the second minute of a resting phase is less than 44 beats, there is a higher risk of death [11].

The examinations with a load (effort, pharmacological provocative tests) designed to assess changes in coronary perfusion and wall mobility of the left ventricle such as SPECT or echocardiography are characterized by relatively high sensitivity and specificity. The latter is especially useful not only to diagnose ischemia, but also to determine a prognosis. Marwick et al. showed a significant difference in the 5-year survival in a group of over 4,000 women, depending on the extent of the ischemic area observed in dobutamine echocardiography [11]. As previously mentioned, given a greater involvement of microcirculation in women when there are no significant changes in the large vessels, a positive result should be carefully interpreted as false. Great hopes for the assessment of coronary perfusion and the regulation of microcirculation are reposed in the methods based on magnetic resonance imaging, which allow depicting coronary perfusion and subendocardial ischemia. Previously published studies demonstrated the usefulness of MRI in the diagnosis of women with coronary ailments and no significant changes in the large coronary vessels. It seems that currently it is the best noninvasive method for diagnosing microvascular coronary dysfunction [5,12,11]. The problem of women with chest pain, abnormal results in stress tests and no significant changes in coronary angiography is not new. In the past, the term “cardiac syndrome X” used to be applied and it was believed that the prognosis was similar to this in the general population. However, results published in the last 10 years questioned this assumption. Gulati et al. showed that the risk of adverse cardiovascular events is 16% in the group of women with no significant stenosis of both symptomatic women, with no changes, compared to 2.4% in asymptomatic women from the general population [5]. In the WISE study, 13% of women with the “normal” coronary angiography resulted died during a 7-year follow-up [1]. 30% of symptomatic women with microvascular dysfunction will develop critical atherosclerotic changes in the coronary vessels within 10 years [12]. Further investigations are necessary to answer the question of whether MCD only affects women, and if so, then how to diagnose this syndrome, how to evaluate the risk and how to treat it.

Treatment

Changes in the therapeutic approach also result from understanding the cause of differences and at least partly discovering pathomechanisms responsible for a different course of atherosclerosis in men and women. Currently offered pharmacotherapy focuses on relieving ailments and the improvement of the endothelial function. Beta-blockers are drugs of proven antianginal efficacy in women, whereas, improvement of tolerance using calcium channel blockers has not been shown. There are no studies that evaluate the role of nitrates. Antidepressin-converting enzyme inhibitors and statins improve endothelial function and the benefits of their use in patients with microvascular dysfunction have been proven [12]. Attempts are being made to use new drugs. It has been shown that imipramine, a tricyclic antidepressant, has a beneficial effect on the symptoms of ischemia, possibly by modulating the perception of visceral pain. Its antiarrhythmic and anti-arrhythmic activity may additionally modulate the microvascular function. Studies on improving the function of small blood vessels during L-arginine supplementation seemed promising, but due to unfavorable results in patients after myocardial infarction, the safety of this substance has been questioned. The MERLIN TIMI-36 and WISE ISCHEMIA studies showed a beneficial effect of ranolazine in women with microvascular dysfunction. However, further studies are necessary to determine the optimal treatment of MCD [12,11].

Apart from drug therapy, the elimination of risk factors and the promotion of a healthy lifestyle play a huge role. The same factors are responsible for the development of atherosclerosis in both women and men. It is important to identify and treat them as soon as possible using lifestyle and pharmacological parameters. It is stressed that women most frequently develop a metabolic syndrome, therefore promoting healthy diet and physical activity among them seems very important. It is a matter of concern that the incidence of smoking grows, especially among young women.

Obesity, diabetes and nicotine use significantly impair the protective effect of estrogens on the cardiovascular system [12].

Summary

Persistent chest pain in women with risk factors for ischemic heart disease is associated with a poor prognosis despite normal results of coronary angiography. Until recently, it was believed that “cardiac syndrome X” did not require special handling. Currently, we are aware of the fact that these patients are at risk of adverse cardiac events and death. Differences in the clinical picture are mainly attributed to changes in the region of microcirculation which occur in women, and are connected with endothelial dysfunction and the abnormal regulation of the subendocardial blood flow. Patients with persistent symptoms of ischemia require precise stratification, which will take into account new elements such as inflammatory markers (hsCRP), the impaired function of small blood vessels (the evaluation of the retinal blood vessels) and exercise capacity. To verify a diagnosis of microvascular dysfunction, it is considered in experienced centers or a method based on magnetic resonance imaging can be used to assess the subendocardial blood flow. There are no in-depth studies that evaluate the effectiveness of treatment. Currently proposed therapeutic regimens include using beta-blockers, statins, angiotensin-converting enzyme inhibitors, tricyclic antidepressants and ranolazine.

References


