



## RELATIONSHIP OF METABOLIC SYNDROME WITH DIFFERENT HEART RATE DISORDERS

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### Resume

The 21st century is the century of impending epidemics, because the number of patients with diseases is increasing: epidemics of chronic heart failure, arterial hypertension (AH), diabetes mellitus (DM) type II, obesity, atrial fibrillation (AF). However, the number of people on our planet is limited, therefore, the likelihood that the same people can be involved in different "epidemics" is quite high. Indeed, we already know relatively much about the relationship, for example, of chronic heart failure and AF, AH and AF. This publication is devoted to another epidemic - metabolic syndrome (MS) [1], especially since MS is directly related to hypertension, diabetes, and obesity.

**Keywords:** hypertension, diabetes, obesity, diabetes mellitus

### Introduction

Is there any relationship between MS and cardiac arrhythmias? Apparently, the answer should be positive, and both with respect to supraventricular and ventricular arrhythmias. So, for example, there are a large number of publications indicating that MS is a factor predisposing to AF, a favorable background for the implementation of risk factors for AF [2]. An example is the study by K. Umetani et al., 2008 [3]. The authors examined 592 patients without obvious structural changes in the heart. Of these, 32 (5%), MS 127 (21%) suffered from paroxysms of AF-atrial flutter. At the same time, paroxysms of AF-atrial flutter were detected in 12 (9%) patients with MS and in 20 (4%) patients without MS. Multivariate regression analysis showed that MS is a significant risk factor for paroxysmal AF-atrial flutter, unrelated to the size of the left atrium ( $> 44$  mm) or age ( $> 70$  years). Of the 5 components, according to the well-known ATP-III (Adult Treatment Panel-III) scale, MS correlated with a high degree of reliability with the risk of paroxysms of AF-atrial flutter, body mass index (BMI) $> 25$  kg / m<sup>2</sup>. Thus, according to the authors, the high risk of AF-atrial flutter in MS may be based on alimentary obesity.





H. Watanabe et al., 2009 [4] conducted a large study, which included 28449 patients, including 3716 (13%) with MS on the ATP-III scale, who did not have AF at baseline. During the observation period (average 4.5 years), AF was registered in 265 people, and the risk of AF in MS was significantly higher. All components of MS, with the exception of elevated triglyceride levels, contributed to this increased risk.

In a study by V.N. Nicolaou et al., 2011 [5], a comparison was made of the size of the atria in patients with and without MS, suffering from nonvalvular paroxysmal AF. Of 60 patients with at least one episode of paroxysmal AF, 26 patients met the ATP-III criteria. In patients with MS, the dimensions of the left atrium were 46.2 mm, without MS - 41.6 mm. The authors conclude that MS may contribute to the onset of AF by increasing the size of the left atrium.

The work of N. Echahidi et al., 2011 [6], in which a large team of authors assesses the risk factors for AF after coronary artery bypass grafting, is very interesting and large-scale. The authors point out that AF is a very common complication after heart surgery, which significantly affects the prognosis. They note that previous studies have already shown that obesity is a risk factor after surgery.

They performed a retrospective analysis of the relationship between obesity and MS, on the one hand, and paroxysmal AF, on the other, in 5085 patients after coronary artery bypass grafting. 1468 (29%) had obesity (BMI > 30 kg / m<sup>2</sup>), 2320 (46%) had MS according to the ATP-III criteria. Paroxysmal AF occurred in 1374 (27%) patients. In obesity, AF paroxysms occurred significantly more often only in patients over 50 years of age. However, MS in the absence of obesity also turned out to be an independent significant risk factor for AF (12% versus 6%), regardless of age. The relationship between an increase in the QT interval and the risk of life-threatening ventricular arrhythmias is well known. In the study by S. Soydinc et al., 2009 [10], it was shown that in 50 patients with MS in accordance with the ATP-III criteria, in comparison with the control group of 33 people, the minimum and maximum corrected QT interval were significantly higher, as well as corrected QT-dispersion.

Another tool for assessing the risk of fatal ventricular arrhythmias is the analysis of heart rate variability, which reflects the state of the autonomic nervous system. As is known, it is the autonomic nervous system that plays an important role in the initiation of malignant ventricular arrhythmias [11].

The probability of their occurrence is usually associated with an increase in the tone of the sympathetic and a decrease in the tone of the parasympathetic nervous system [12]. In the work of S.K. Park et al., 2009 [13], 423 elderly men were examined (Normative Aging Study), of which 32% had MS.





Thus, we have reason to believe that the presence of MS increases the risk of AF and life-threatening ventricular arrhythmias in patients. On the other hand, MS is clearly not one of the diseases that lie in the field of vision of those cardiologists who are specifically engaged in the diagnosis and treatment of cardiac arrhythmias, that is, arrhythmologists. Information about the pathogenesis of MS is directly related to the pathogenesis of arrhythmias in this disease, and the principles of MS treatment are related to the primary prevention of cardiac arrhythmias.

In other words, when using different definitions depending on ethnicity and gender, the frequency of MS can vary within 24%. But, regardless of the criteria applied, the results of all studies indicate the adverse consequences of "concentration" in one patient of one or another combination of cardiometabolic risk factors.

. H.M. Lakka et al., 2012 [19], using either the ATP III criteria or the WHO criteria, identified a group of 1209 middle-aged men and followed her for eleven years; the presence of MS, established in accordance with any of the criteria used, increased the relative risk of death from cardiovascular causes by 2.5-4 times. In addition, according to the calculated data in the population of sixty-year-olds, the prevalence of MS can reach 40% [20]. It is not surprising that, from the point of view of WHO experts, MS is one of the ten most dangerous diseases of modern mankind [21]. In accordance with the general medical significance, the problem of MS is discussed by specialists of various profiles: there are sections on MS both in the European guidelines on primary prevention of cardiovascular diseases, and in the guidelines for the management of patients with hypertension from 2007, and in a document discussing the relationship between diabetes, pre-diabetes and cardiovascular disease. Moreover, in the fall of 2007, Russian recommendations were published, completely devoted to the diagnosis and treatment of MS. This document contains another version of the criteria for detecting MS [22]. In June 2007, within the framework of the 76th Congress of the European Society for the Study of Atherosclerosis, a satellite symposium "Metabolic Syndrome" was held. In all speeches, the importance of the subject of discussion was emphasized, but at the same time the thesis was repeatedly voiced that something that has at least 20 definitions cannot be a diagnosis. But even if we are not talking about a diagnostic formula, the identification of metabolic distress factors is an alarm signal that requires active action. Activity concerns both examination and treatment. When one or several of the most obvious components of MS are identified - abdominal obesity (especially in persons without obesity), dyslipidemia, disorders of carbohydrate metabolism, hypertension - a targeted search for other possible manifestations of it is necessary - hyperuricemia, left ventricular hypertrophy, micRoalbuminuria, an increase in the speed of propagation of the pulse wave - factors





that not only confirm an unfavorable prognosis, but also determine the choice of therapeutic tactics in general, and preferences in relation to groups of drugs and specific drugs, in particular ...An example is the changing attitude towards isolated office hypertension. By definition, isolated office hypertension can be talked about if re-detection of blood pressure values above 140/90 mm Hg during visits to the doctor, not confirmed by the results of 24-hour blood pressure monitoring. It is known that in the absence of target organ damage, the prognosis in these people is much better than in patients with stable hypertension, although it may be slightly worse than in people with completely normal blood pressure. A calm attitude to this phenomenon was associated with this fact... However, in the new version of the European recommendations for the management of patients with hypertension, it is indicated that it is necessary to assess, in addition to the damage to target organs, also metabolic risk factors, since their identification entails the obligation not only to correct the patient's lifestyle and dynamic monitoring him, but also medical correction of the identified violations.

The inclusion of MS in the criteria for stratification of the risk of cardiovascular complications in patients with hypertension naturally suggests its influence on the choice of therapeutic tactics.

So, if signs of MS are detected in a person with normal blood pressure, then maximum efforts should be made to correct his lifestyle. At high normal values of blood pressure, in addition to non-drug measures, the indication of antihypertensive therapy should be considered; AH of I and II degrees is an unconditional indication for the appointment, following the correction of lifestyle, drugs that normalize blood pressure; with grade III hypertension, drug recommendations may precede the development of a program of non-drug effects.

The appearance of a patient with MS is often an illustration of a disregard for a healthy lifestyle. Meanwhile, it is in patients with signs of MS that lifestyle correction can be especially effective. Weight control is key in the non-drug program in this patient population, as weight loss to normal levels significantly lowers their risk of developing diabetes. Moreover, it is known that a decrease in the total body weight by 10% ensures a decrease in the mass of visceral fat by about 30%. Meanwhile, it has now been proven that visceral fat is not an inert storage of energy, but a real endocrine organ [23], producing about 20 biologically active substances, expressing a number of receptors capable of responding to various neurohumoral signals. As a result, this "organ" is in constant metabolic interaction with other organs and systems, influencing eating behavior, carbohydrate and lipid metabolism, performing neurohumoral and immune functions. Naturally, weight control can be carried out





successfully only with an integrated approach: a healthy diet plus sufficient physical activity.

An impressive illustration of this is the results of the Nurse Health Study (2013): with the same BMI, mortality in the groups with moderate and high physical activity was significantly lower than with low physical activity.

It is clear that for someone the most acceptable will be "natural" physical activity at work (refusal to take the elevator in favor of walking up the stairs, 5-7 km of walking to work and / or home, etc.), who prefers to work out in the gym or in the swimming pool. In some cases, even an integrated approach does not provide the necessary weight loss. The only drug today that can effectively and safely influence this process from the point of view of the cardiovascular system is Xenical - a selective inhibitor of gastrointestinal lipases. According to the Russian guidelines for the diagnosis and treatment of MS, indications for drug therapy of obesity are BMI > 30 kg / m<sup>2</sup> or a combination of BMI > 27 kg / m<sup>2</sup> with signs of abdominal obesity, an inherited predisposition to type 2 diabetes or its presence, dyslipidemia, AG.

However, the European guidelines for the management of patients with hypertension in 2007 specifically emphasize that, first of all, drugs should be used that do not increase the risk of developing new cases of diabetes.

This is due to the fact that an assessment of the dynamics of the spread of diabetes around the world allows us to talk about a real epidemic of this disease: if the current trend continues, then by 2010 there will be about 221 million patients with diabetes on Earth, and by 2030 - 360 million [25]. Since in a number of clinical studies comparing the efficacy and safety of therapy with "old" (diuretics and beta-blockers) and "new" (angiotensin-converting enzyme inhibitors (ACE inhibitors) and ARBs) drugs, data were obtained on the more rare development of new cases of diabetes in the treatment of the latter, it was concluded that hyperactivation of the renin-angiotensin-aldosterone system plays a leading role in the development of clinically significant disorders of carbohydrate metabolism. At the moment, it has been proven that this class of drugs has an antihypertensive effect comparable to other modern drugs that lower blood pressure, and a side effect profile comparable to that of placebo. The therapeutic niche occupied by this group of drugs is rapidly expanding and currently includes chronic heart failure, past myocardial infarction, diabetic nephropathy, proteinuria / microalbuminuria, left ventricular hypertrophy, AF, MS [26]. In accordance with the versatility of MS, therapy for this condition can only be complex, multicomponent. At different stages, different manifestations of MS may come to the fore in different people. Therefore, when treating these patients, it is advisable to prescribe, first of all, therapy aimed at correcting the currently leading





symptom (be it hypertension, dyslipidemia or hyperglycemia), and within the framework of the chosen direction, the characteristics of a particular patient should be taken into account.

If we consider that the combination of any level of increased blood pressure and metabolic disorders causes a high or very high risk of cardiovascular complications, and risk III and risk IV are absolute indications for the initial appointment of combined antihypertensive therapy, then it is fundamentally important to emphasize that in almost any case of assisting a patient with MS, we will talk about the simultaneous appointment of an ACE inhibitor / ARB + calcium channel blocker ± an agonist of I-1-imidazoline receptors ± P-blocker ± indapamide / hydrochlorothiazide (no more 12.5 mg / day). In the course of a population study carried out in Finland, it turned out that over the past 10 years of the 20th century, the Finns as a nation have become much more "metabolically burdened" - the number of people with excess body weight, lipid metabolism disorders, has also increased significantly. Time of blood pressure on average became lower. This suggests that at the population level, as in individual individuals, at a particular moment, various components of the MS may predominate. Accordingly, at a particular stage, for example, not antihypertensive, but only lipid-lowering therapy may be required. The proportion of diabetes mellitus in terms of worsening unfavorable prognosis in patients with MS is extremely large. For example, North American Indians who did not have diabetes did not have an increased risk of MS. In elderly Italians with diabetes, the risk ratio of complications did not differ between those with other signs of MS and those without: the increase in risk due to dyslipidemia was "extinguished" by the actual diabetes. As emphasized in the Russian guidelines for the diagnosis and treatment of MS, the results of numerous studies indicate the importance of not only diabetes mellitus, but also IGT, especially postprandial hyperglycemia, for cardiovascular morbidity and premature mortality. Adequate glycemic control (in accordance with the target program "Diabetes mellitus" - fasting glucose <5.5 mmol / L; postprandial glucose <7.5 mmol / L) is the cornerstone of reducing cardiovascular risk in these patients.

### Summary

The drug of first choice for controlling glycemia in MS, at least in overweight patients with diabetes, is metformin. It was assumed that the above positive properties would make metformin useful already at the stage of NTG.

However, when directly comparing the effectiveness of only non-drug measures and only the use of metformin, it turned out that in order to prevent one new case of diabetes, half the number of patients should be treated non-drug than with





metformin. Moreover, while adhering to non-drug recommendations and taking metformin, the result did not improve [27].

Taking into account the negative prognostic value, it is advisable to include aspirin in the complex drug therapy of most patients with signs of MS, and even more so in the presence of diabetes, for the purpose of primary prevention of ischemic heart disease. Thus, although there is no reason to consider MS as a separate disease, of course, this is not a set of random risk factors, since all the manifestations currently referred to as MS manifestations are in a pathogenetic relationship with each other. The concept of MS is useful for the formation of an integrated approach to the diagnosis, prevention, effective and safe therapy of cardiovascular diseases. The choice of therapeutic tactics should be determined by the set of MS components in a particular patient.

The question of whether MS is an independent risk factor for AF or whether this risk consists of the contributions of individual components of MS remains open. It is he who, in particular, is discussed in the editorial article of the journal "Circulation" [28], dedicated to the publication of H. Watanabe et al. [4] on the relationship between MS and FP. The authors of the editorial believe that in any case, the success of the prevention and treatment of AF in MS will depend on adequate treatment of hypertension, diabetes mellitus, obesity, obstructive sleep apnea syndrome, that is, on the primary prevention of AF. This approach to treatment is reflected in the most important recent publications on arrhythmias: the ACC / AHA / ESC guidelines for the diagnosis and treatment of AF [29] and the ACC / AHA / ESC guidelines for the treatment of ventricular arrhythmias and the prevention of SCD [30]. So, for the first time, perhaps, in the new guidelines on AF, based on the results of a number of multicenter studies (HOPE, LIFE, etc.), it is proposed to use ACE inhibitors and ARBs for the primary prevention of AF. As for ventricular arrhythmias, the only group of drugs for which the effect on the "endpoints" (reducing the risk of SCD) is absolutely proven are  $\beta$ -blockers.

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