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EFFECTS OF INTENSIVE HYPOGLYCEMIC THERAPY FROM THE POSITION OF THEIR INFLUENCE ON THE DEVELOPMENT OF HEART RHYTHM DISORDERS

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Abstract: It is known that DM 2-4 times increases the risk of CVD, and mortality when combined increases 4-5 times. The combination of a cluster of risk factors for the rapid development and progression of atherosclerosis, which is based on insulin resistance - hyperglycemia, dyslipidemia, hypertension, allowed the expert Commission of the National educational program of the United States cholesterol (NCEP) to equate DM2 risk to coronary heart disease. This article reviews the literature on the relationship of diabetes and hypoglycemia with the development of cardiac arrhythmias.

Key words: atrial fibrillation, diabetes mellitus, hypoglycemia, prevention

CVDs remain the leading cause of death worldwide, they are responsible for 17.3 million deaths annually - 31.5% of all deaths of the world population and 45% of all deaths from NCDs, which include 4 groups of diseases, including cardiovascular, cancer, bronchopulmonary and diabetes mellitus (DM) [2].

However, the XXI century was marked by an epidemic of metabolic risk factors of CVD, such as obesity, impaired glucose tolerance, diabetes mellitus (DM). According to the International Diabetes Federation (IDF, 2014) currently 400 million people in the world suffer from diabetes and by 2035 their number will increase to 600 million people. In Russia, by 2030, the number of patients with diabetes is predicted to increase to 14 million. It is known that diabetes 2-4 times increases the risk of CVD, and mortality when combined increases by 4-5 times [3]. The combination of a cluster of risk factors for the rapid development and progression of atherosclerosis, based on insulin resistance - hyperglycemia, dyslipidemia, arterial hypertension - allowed the expert committee of the US National Cholesterol Education Program (NCEP) to equate type 2 diabetes with coronary heart disease. Today, T2DM is considered the equivalent of having clinically significant CVD [1].

Well-known prospective studies have confirmed the role of hyperglycemia in the development of CVDs (DECODE, EPIC-Norfolk, ARIC, ADVANCE). However, a number of studies have shown that despite improved glycemic control, macrovascular complications and associated CVDs continue to progress in DM2 patients (UKPDS, Kumanato Study)

Glycemic control studies have shown that intensive glycemic control in the two types of diabetes does not always have similar effects. The Diabetes Control and Complications Trial (DCCT) has convincingly demonstrated the positive role of intensive glycemic control in reducing the risk of micro- and macrovascular complications in patients with type 1 diabetes. It was shown that strict and constant glycemic control (average HbA1c level ~ 7% for 6.5 years) is the main prevention of the development and progression of microvascular complications and reduces the frequency of microalbuminuria by 39%, proteinuria - by 54%, neuropathy - by 60% [20].

The target HbA1c level, according to the current consensus of the European Association for the Study of Diabetes and the American Diabetes Association, is less than 7.0% (with normal values less than 6.0%).

Microvascular complications are known to be the cause of early disability in patients with type 2 diabetes, whereas macrovascular complications in the form of cardiovascular disease are the cause of death in eight out of ten patients [7, 9]. According to Veterans Affairs Diabetes Trial (VADT) data, severe hypoglycemic reactions in DM 2 are one of the main predictors of myocardial infarction, cerebral stroke and death from all causes [3]. The ambiguous role of intensive glycemic control was demonstrated by a large-scale multicenter randomized two-factor ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, the key point of which was to maintain diabetes compensation with glycosylated hemoglobin (HbA1c) levels less than 6.5%. The study included 10251 high-risk patients with type 2 DM, randomized into intensive (HbA1c less than 6%) and traditional (HbA1c 7.0-7.9%) glycemic control groups with different intensity of control of blood pressure and lipid profile.The study was terminated early due to high mortality in the intensive treatment group (257 deaths, mean HbA1c 6.4% versus 203 deaths, mean HbA1c 7.5% in the traditional treatment group, i.e., 54 excess deaths in the intensive treatment group) [16]. As a careful review of the study results showed, episodes of hypoglycemia were significantly more frequent in the intensive glycemic control group (10.5% vs 3.5%). At the same time, a statistically significant reduction in myocardial infarction, stroke, and CV mortality was observed in the group of patients without CVD with baseline HbA1c<8.0% [3]. The effect of intensive glycemic control on reducing the risk of microvascular (nephropathy and retinopathy) and macrovascular (myocardial infarction, stroke, CC mortality) complications was demonstrated in the ADVANCE (The Action in Diabetes and Vascular disease preterAx and diamicroN-MR Controlled Evaluation) study (OR 0, 9 [95% CI 0.82-0.98] p=0.01), but it should be noted that the reduction in risk of microvascular events (OR 0.86 [95% CI 0.77-0.97], p=0.01) was significantly higher, whereas the reduction in risk of macrovascular events did not reach the level of statistical significance (OR 0.94 [95% CI 0.84-1.06], p=0.32). However, in contrast to the ACCORD study, no increase in total or CV mortality was observed in the intensive glycemic control group compared to the standard glycemic control group [4].

Later, the results of the VADT study confirmed those of the ADVANCE study, where there were no differences in the incidence of CV events between the intensive and standard glycemic control groups (OR 0.88 [95% CI 0.74-1.05], p=0.12). CVD mortality in the intensive glycemic control group was slightly higher than in the standard glycemic control group (38 versus 29, sudden death 11 versus 4), but this difference did not reach statistical significance. An in-depth analysis of the results showed the effect of the duration of diabetes disease on the incidence of endpoints. Thus, when the history of diabetes was not longer than 12 years, intensive glycemic control did not demonstrate its negative effect on CV mortality.

At the beginning of the 21st century Nordin C. expressed an opinion about proarrhythmogenic effect of hypoglycemic reactions due to the direct effect of hypoglycemia and catecholamine reactions, causing hypokalemia and other disorders [13].

A number of studies have demonstrated an independent role of DM in the development of sudden death (SD) [5].

Several mechanisms may be involved in the development of sudden death against the background of hypoglycemia. An important pathogenetic link is the development of the so-called "autonomic dysregulation disorder associated with hypoglycemia" (NARSH). NARSH is a form of sympathoadrenal system failure as a result of a recent episode of

iatrogenic hypoglycemia, which leads to a lower blood glucose threshold level that triggers the counterinsulatory response necessary to restore normoglycemia [18]. This contributes to an almost 25-fold increase in the risk of severe hypoglycemia against the background of intensified insulin therapy and the appearance of repeated episodes of hypoglycemia.

The Pearson E.C. study found an association between DM and prolongation of the PQ interval in patients with coronary heart disease (CHD) [15]. Older age and the presence of comorbidities determine the greatest risk of cardiovascular complications associated with hypoglycemic states in type 2 DM. At blood glucose levels < 3 mmol/l for more than 30 min, increased QTc time and ventricular tachycardia occur with an increased risk of ventricular fibrillation and VS. Abrupt changes of mean amplitude of glucose excursion (MAGE) more than 5 mmol/l contribute to greater vulnerability of electrical stability of the heart, especially in weakened patients with the presence of coronary heart disease and autonomic dysfunction.

The independent role of diabetes in the development of AF was assessed in the Fremingham study [21]. Numerous studies since then have found that AF in people with diabetes is at least twice as common as in people without diabetes, and 3 times as common if, in addition to diabetes, AH is present [14].

The ADVANCE study demonstrated the role of AF as a strong independent marker of total and cardiovascular mortality, as well as severe chronic CHF in DM patients [7], which required more intensive control of blood pressure and other cardiovascular risk factors in the study population of patients.

So what is the determining role of DM in the development of FP?

Cardiac muscle damage in DM2 is determined not only by atherosclerotic lesions of the coronary arteries, but also by specific changes peculiar to "late" complications of diabetes (microangiopathy, neuropathy). Based on pathological anatomical studies Rubler S. et al. [1972] proposed the term diabetic cardiomyopathy (DC), characterized by the clinical picture of dilated cardiomyopathy with the development of heart failure with low ejection fraction in diabetic patients in the absence of arterial hypertension and coronary artery atherosclerosis. DC is a pathology of the heart muscle, manifested by a wide range of biochemical and structural abnormalities, mediated by insulin resistance, hyperglycemia, impaired free fatty acid metabolism and increased free radicals.

Diastolic dysfunction of the left ventricle (LV) is considered as an early marker of myocardial damage in DM2, noting the pathogenetic relationship between LV diastolic dysfunction and LV hypertrophy (LVH) in the development and progression of chronic heart failure (CHF), which in turn contributes to the formation of arrhythmogenic substrate [11]. The pathogenetic role of glycometabolic processes in the development and progression of diastolic abnormalities is associated with the formation of hypertrophy under the influence of insulin resistance and activation of fibrosis processes against the background of hyperglycemia [17].

To date, there are still discussions on the topic - should diastolic dysfunction and autonomic cardiovascular neuropathy be combined into a single concept, or is there still a need to distinguish between these mechanisms?

Another key point explaining the high risk of AF in DM is the results of studies of purely electrophysiological interest. Aleksandrov A.A. et al. [2011] explain the formation of electrophysiological remodeling of ion channels of myocardiocyte sarcolemmal membrane in DM patients by the presence of a transmembrane phosphoinositol mechanism, which normally represents a kind of glucose transport mechanism that is activated when insulin binds to the cell receptor, or when sulfonylurea derivatives interact with the cellular component of phospholipase C (FLC). The resulting

diacylglycerol (DAG), by stimulating pyruvate kinase C (PKS), increases the availability of glucose transporters and promotes glucose diffusion inside the cardiomyocyte. At the same time, electrolyte fluxes of the cardiomyocyte are formed, providing the correct action potential of the myocardial cell, periods of its electrical refractoriness (KATP-dependent channels, Ca-balance, Na/H-exchange). Electrophysiological activity of ion channels is dramatically impaired by the processes of insulin resistance and/or lack of insulin.

The high risk of electrophysiological abnormalities in DM is associated with the overload of cardiomyocytes with Ca2+ ions. Against the background of a sharp decrease in glycolysis, the sarcoplasmic reticulum loses the ability to absorb calcium at the normal rate. This in turn leads to an imbalance between the mitochondria's need for ATP to pump out protons as protection against excess calcium and its amount. Thus, myocardial contracture is formed, conjugation of myocardial electrophysioo logical and contractile processes is disturbed. In the works of Z.H. Lu et al., high levels of HbA1 were associated with increased risk of atrial fibrillation recurrence in patients with type 2 DM and paroxysmal AF who underwent catheter ablation [12].

At the same time, the effect of hypoglycemia on increased risk of cardiac arrhythmias is currently not confirmed in randomized clinical trials.

Thus, in the ACCORD study, where 10082 patients were selected, intensive glycemic control did not demonstrate its effect on the development of AF. Similar results were obtained by researchers Nicolas G.A. et al. where hypoglycemia was associated with the development of AF only in female patients.

In later studies, it was demonstrated that DM in need of pharmacological control by 40% increased the risk of PD, as well as the risk of PD was associated with the duration and lack of adequate glycemic control.

The Chang Sh. study found a positive role of metformin monotherapy in reducing the risk of AF in patients with diabetes. The authors attribute this effect to a decrease in tachyinduced cell myolysis and oxidative stress.

In a study by E. Chow et al. studied the effect of hypoglycemic episodes on the incidence of various types of LDCs. The study included 25 patients with type 2 diabetes receiving insulin therapy. All patients had atherosclerotic lesions of the cardiovascular system (CHD, peripheral arterial lesions or cerebrovascular disease), as well as risk factors in the form of obesity, smoking, and hypodynamia. All patients underwent long-term glucose-cardiac monitoring for 5 days. Hypoglycemia was established at HbA1c?3.5 mmol/l. During the observation period, 14 patients had episodes of hypoglycemia with a total duration of 134 hours. At the same time, the duration and frequency of nocturnal hypoglycemia prevailed over daytime values. A comparative analysis of HRs for eu- and hypoglycemia showed that bradycardia was 8 times more frequent in nocturnal episodes of hypoglycemia (OR 8.42 [95% CI 1.40-51.0]). Noteworthy is the fact that despite the presence of daytime episodes of hypoglycemia, bradycardia was not recorded during these hours. AF was 4 times more frequently observed in hypoglycemia (3.98 [1.10-14.4]), but without significant differences between its frequency in daytime and nighttime. Ventricular extrasystole was recorded with equal frequency during hypoglycemia, both during the day (1.31 [1.10-1.57]) and at night (3.06 [2.11-4.44]). The analysis of the heart rhythm variability condition showed its reliable decrease, as well as a decrease in the total power of the spectrum, an increase in the strength of high-frequency components. Episodes of hypoglycemia contributed to a significant increase in the corrected QT interval predominantly in the daytime.

Researchers have concluded that the mechanisms of ventricular tachyarrhythmias during daytime and nighttime hypoglycemia are different. Thus, prolongation of the QT

interval in the daytime may lead to an increase in trigger activity, a form of early postdepolarization. Sympathetic activity and cytosolic calcium overflow, in turn, leads to prolongation of postdepolarization and development of ventricular extrasystole. The two mechanisms described probably explain ventricular HRV predominantly during daytime hypoglycemia. Nevertheless, the vast majority of LDCs occurred during nocturnal hypoglycemia, when sympathetic system activity is not pronounced. Researchers found the answer to this question in experimental hypoglycemia. In response to increased vagus system activity and decreased sinus node activity, especially in the presence of NARSH, latent rhythm drivers are activated, which explains the frequent development of AF and ventricular extrasystole at night. Ventricular extrasystole against a background of bradycardia is highly likely to be a trigger for Torsade de Pointes, which has been demonstrated in previous studies in patients with hypoglycemic coma. Summarizing their results, the authors emphasize that in this study, despite the lack of intensive glycemic control, episodes of hypoglycemia occurred with approximately the same frequency as in studies with intensive glycemic control and call for cardiologists and endocrinologists to more carefully perform risk-stratification of patients with a high risk of cardiac arrhythmias and, therefore, with the risk of a fatal outcome.

A relatively new study on the effect of hypoglycemia on the risk of AF was the work of Ko S.H. et al. [9]. Using a retrospective analysis of the case histories of more than 2 thousand patients with type 2 diabetes without prior AF, it was found that hypoglycemia is an independent predictor of AF within 5 years of follow-up in patients with type 2 diabetes even in the absence of CVD. But it should be noted that this study was retrospective and studied only cases of documented hypoglycemia, that is, when patients seek medical care, while the vast majority of episodes of hypoglycemia are asymptomatic. And the development of AF was also diagnosed when it was detected during a standard ECG, that is, episodes of paroxysmal AF might have been missed.

The study of the role of hypoglycemia in the increased risk of cardiovascular death is complicated by the absence of specific anatomical and morphological markers of hypoglycemia and by the fact that when acute cardiac pain occurs, the patient does not always determine the glycemic level and/or fix posthypoglycemic hyperglycemia. It is these factors that limit the analysis of existing studies and make it difficult to design a study that can prove or disprove the effect of hypoglycemia on arrhythmia risk.

Given the growing incidence of diabetes and associated AF, which in turn increase the incidence of cardiovascular complications in the form of strokes, heart failure, inevitably leading to disability and increased mortality, the problem of safe hypoglycemic therapy and the development of methods for its optimal control will only increase its relevance. The problem of interaction between antiarrhythmic, hypoglycemic and antiplatelet drugs also requires detailed coverage, which will serve as a basis for new research in the future.

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