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ROLE OF PECTINATE MUSCLE IN THE MORPHOFUNCTIONAL REGULATION OF THE CONTRACTILE ACTIVITY OF THE HEART: A REVIEW

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The pectinate muscles are located on the inner surface of the right and left atria, but their functional significance remains unknown. This review describes the development of pectinate muscles at the molecular-genetic level, the features of ion channels and intercellular connections that allow pectinate to provide rapid conduction of excitation for the coordinated work of the atria and examines the influence of pectinate muscles on the development of atrial fibrillation.

Key words: pectinate muscles; electrophysiology; atrial arrhythmia; atrial fibrillation; cardiac anatomy

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At the present stage of development of medical science, the fundamental problem of investigation of the functional anatomy of the heart is given great attention by both theorists and clinicians, since diseases of the cardiovascular system are associated with the most common causes of mortality in the world, i.e., coronary heart disease and stroke [1, 2]. The heart conduction system is of particular interest, which, performing the rhythmic coordination of the activity of the myocardium of individual chambers of the heart, ensures stable functionally optimal operation of the heart pump throughout the life of the body [3]. Disorders of the heart conduction system can play a role in the development of diseases that lead to a deterioration in the patient's quality of life, disability and, in severe cases, to death.

Disorders of conduction and excitability of the myocardium leads to the atrial fibrillation (AF), which is the most common type of supraventricular tachyarrhythmia with chaotic electrical activity of the atria, precluding their coordinated contraction [4]. In 2010, 8.8 million adults over the age of 55 in the European Union suffered from AF, and according to forecasts, this number will double to 17.9 million by 2060 [5]. In Russia, in 2010, 2.5 million cases of AF were registered per year, while by 2017, the incidence increased to 3.7 million [6]. AF is known to increase the risk of stroke by 5 times and at the same time the course of the disease has an unfavorable prognosis [7]. As far as is known at present, AF develops and persists due to the presence of a factor (trigger) that triggers arrhythmia and electroanatomic substrates that support it, being the focus of circulation of the re-entry of excitation [8]. Indeed, pectinate muscles located on the inner surface of the right atrium can also be attributed to such structures, since they are able to initiate and maintain the re-entry of excitation [9]. However, their functional significance and interaction with the conduction system of the heart remain poorly investigated.

The purpose of this review of the available literature is to clarify the role and degree of influence of the pectinate muscles on the excitation and regulation of contractile activity of the right atrium, as well as to determine the features of the anatomy of these structures, which can lead to the occurrence of AF when impaired.

ANATOMY OF THE CONDUCTION SYSTEM OF THE HEART

The heart is a hollow muscular organ that receives blood from the veins flowing into it and pumps blood into the arterial system. The atria of the heart have hollow processes, i.e., the right and left auricles (appendages) of the atrium, which cover the base of the aorta and the pulmonary trunk. Conduction system, formed by specialized cardiomyocytes, whose structural components are involved in generating and conducting excitation, plays an important role in the contractile activity of the heart and in the coordination of the musculature of the individual chambers of the heart. Conduction system of the heart include nodes and bundles. The central elements of the conduction system of the heart are: 1) sinoatrial node (sinus node, Keith-Flack node), which is in the wall of the right atrium near

the opening of the superior vena cava; it provides rhythmic contraction of the atria, being the first order pacemaker; 2) atrioventricular node (Aschoff-Tawara node), located above the attachment site of the septal cusp of the tricuspid valve. The fibers of this node, directly connected to the atrial muscles, continue into the intraventricular septum, forming an atrioventricular bundle (His bundle), i.e., the pathway of excitation from the atria to the ventricles, which in the ventricular septum is divided into two branches going to the right and left ventricles, respectively. These branches of the His bundle pass under the endocardium, branch widely and end in a network of Purkinje fibers [10].

GAP JUNCTIONS OF CARDIOMYOCYTES IN THE HEART CONDUCTION

Thanks to the ability to conduct excitation at a high rate, Purkinje fibers ensure synchronous contraction of the ventricles: firstly, the interventricular septum is excited, then the apex of the heart and only after that the basal ventricles. This functional feature is due to the expression of unique ion channels in the gap junctions of cells, i.e., connexin 40 and connexin 43 [11, 12]. Gap junctions are a type of connection of cells that consist of two protein half-channels called connexons. In turn, each connexon is a set of six connexin proteins that form pores for the formation of a gap channel between the cytoplasm of two adjacent cells. This channel provides a bidirectional flow of ions and signaling molecules. Connexins are designated by the abbreviation Cx, followed by the designation of the molecular weight in kDa; for example, a connexin with a molecular weight of 40 kDa is designated as Cx40 [13]. Three main connexin isotypes are expressed in the heart, i.e., connexin Cx40, Cx43 and Cx45. They differ in the expression area and the amount of ion conductivity [14, 15]. As shown in literature, mutations of connexin genes and changes in the expression of the distribution of Cx40, Cx43 can be factors in the development of AF [16, 17]. Based on data on a decrease in connexin expression in AF, O. Bikou et al. (2011), using an adenoviral vector with Cx43, increased the expression of Cx43 in the porcine atrium, which led to an increase in conductivity and prevention of AF development [18]. Based on this study, it seems likely that connexins can be used as therapy for AF in the future. In addition, regarding the heart conduction system, the isotypes of connexins expressed in different areas of the heart should be considered.

EMBRYOLOGY OF THE CONDUCTION SYSTEM OF THE HEART AND PECTINATE MUSCLES

For a comprehensive assessment of the relationship between the pectinate muscles and the heart conduction system, the embryogenesis of the heart should be discussed in more detail. The heart develops from two bilateral fields in the embryonic mesoderm, which merge along the midline and form a primary cardiac tube lined from the inside with an endocardium, and from the outside with a myocardium consisting of two layers of cells. The space between them is filled with a thick basement membrane, the so-called “cardiac jelly” [19]. As soon as the heart begins to contract on the 21st-22nd day of embryogenesis, a rapid growth of the heart tube occurs, which leads to a change in its shape. At this stage, heart has the following structures: the venous sinus, followed by the venous division, the arterial department (primary ventricle) and then the arterial trunk [20, 21].

As described by D. Sedmera et al. (2008), the development of the myocardium of the heart occurs in stages. At the first stage, in the early tubular heart, the heart wall consists of 2-3 layers of epithelial-like myocardium, “cardiac jelly” and endocardium. In the second stage, corresponding to the end of the fourth week of pregnancy, the characteristic protrusions of the myocardium, i.e., trabeculae, form. The third stage is the compaction of the basal areas of these trabeculae, which correlates with the ingrowth of the coronary vascular system from the epicardium and corresponds to weeks 10-12 of pregnancy. The final stage is the development of a multilayer spiral system of ventricular myocardium fibers at the 4th month of pregnancy [21, 22]. From trabeculations in the ventricles, muscle cords, i.e., trabeculae, papillary muscles and networks of Purkinje fibers, are formed. Pectinate muscles develop from trabeculations in the atria; of note, trabeculations appear earlier in the right atrium than in the left atrium [23].

Based on his research, D. Sedmera et al. (2008) describes the development of pectinate muscles as follows: pectinate muscles appear in the future auricles of the atria after the formation of the atrial septum and perform a dual role. They, firstly, strengthen the rather thin wall of the atrium, similar to umbrella frames, and, secondly, serve as a morphological substrate of preferred conduction pathways, which probably exist to ensure synchronous activation and contraction of the atria, and not for the rapid conduction of impulses between the sinoatrial and atrioventricular nodes. Similarly, this fact was confirmed in studies of excitation in the atria in chickens [21, 22, 24].

Thus, it can be concluded that pectinate muscles perform a similar function to Purkinje fibers; however, this fact is not fully described in the literature, so a more detailed study and morphofunctional analysis of the development of these heart structures during embryogenesis at the cellular and molecular level is required.

GENETIC REGULATION OF EMBRYOGENESIS OF THE HEART CONDUCTION SYSTEM

The myocardial cells of the primary cardiac tube do not have gap junctions and have a poorly developed sarcoplasmic reticulum, so they have automatism, slow conductivity and poor contractility. In the process of growth and division of the cardiac tube into chambers, differentiation of myocardial cells occurs due to the expression of a genetic program characteristic of cardiac chambers. This program controls the development of the myocardium of the heart chambers, as a result of which the cells acquire gap junction proteins (Cx40, Cx43) and sodium channels (Scn5a), aimed at ensuring high conductivity and contractility of the myocardium [25]. T box (Tbx) transcription factors, which are expressed in various parts of the heart, plays an important role in the differentiation of cardiomyocytes. Thus, factors Tbx5 and Tbx20 function in the early cardiac tube, activating the genetic program of differentiation of the myocardium of the heart chambers, while fac-

tors Tbx2 and Tbx3 contribute to the development of the conduction system [26-28]. Most arrhythmogenic regions in the adult heart arise from those regions of the embryonic heart where this genetic program does not provide proper differentiation; Tbx3 expression regions are especially susceptible [29, 30].

As described by D.S. Park et al. (2017), rapid conduction is a distinctive feature of the formation of the heart chambers, where the pectinate muscles of the atria and the trabeculated myocardium in the ventricles "gather the phenotype of rapid conduction". The subendocardial cardiomyocytes of the trabeculae in the ventricles undergo further differentiation with the subsequent formation of highly specialized Purkinje fibers, whereas the pectinate muscles in the atria retain the phenotype of rapid conduction without additional differentiation. It is known that the properties of the slow conduction of the nodes of the heart conduction system are determined by the almost complete absence of the pore-forming subunit of the cardiac sodium channel NaV1.5 (encoded by Scn5a) and the predominant expression of proteins with low conductivity Cx30.2 and Cx45 (encoded by Gjd3 and Gja7, respectively) [31]. In contrast, tissues with fast conduction, such as atrial myocardial pectinate muscles and Purkinje fibers, are enriched with NaV1.5 and Cx40 and Cx43 proteins with high conductivity and gap junctions (encoded by Gja5 and Gja1, respectively) [31].

The study of M.C. Bressan et al. (2014) confirms that the development of pectinate muscles correlates with an increase in the overall velocity of excitation conduction, while the areas with pectinate muscles were accompanied by the expression of Cx40 and Nav 1.5, due to which the formation of channels of a larger diameter for the propagation of the action potential occurs. A similar expression of Cx40 and Nav 1.5 is observed in the development of the Purkinje network in the ventricles. Similarly, this study demonstrated that stretching of the myocardium of developing atria leads to an increase in the expression of fast conduction proteins (Cx40, Nav 1.5) [32].

The study performed by A. Shekhar et al. (2016) demonstrated that the same transcription factor ETV1 is expressed in the region of pectinate muscles in the atria and Purkinje fibers in the ventricles, which regulates the expression of Nkx2-5, Gja5 and Scn5a, key cardiac genes necessary for rapid conduction. ETV1-deficient mice showed pronounced cardiac conduction defects in combination with abnormalities in the development of Purkinje fibers, including the His bundle branch blocks [33].

Thus, the functional significance of the pectinate muscles in the developing heart is the regulation of synchronous atrial contractile activity, which correlates with the expression of proteins of cellular compounds and channels Cx40, Cx43 and Nav 1.5, providing rapid conduction of excitation.

ASSOCIATION BETWEEN THE PECTINATE AND THE TERMINAL CREST

Considering the association between the conduction system and the pectinate muscles, another important anatomical structure, the terminal crest or crista terminalis, from which the pectinate muscles begin, should be discussed. Tachycardia, called "Cristal Tachycardias", can be initiated in this area [34]. In a normal atrium, the terminal crest functionally and morphologically differs from the pectinate muscles by a large amount of collagen, another type of expressed connexins, and other cellular compounds [35]. However, a number of animal studies have found cells with pacemaker activity in the terminal crest, which can become dominant in the pathological settings [36, 37]. Of note, some researchers attribute these clusters of cells with functional characteristics similar to those in the sinoatrial node to the "paranodal area" or are called "subsidiary atrial pacemaker" [36, 38]. R.S. Stephenson et al. (2017) demonstrated an association between the paranodal area and the pectinate muscles, which was shown on computed tomography images of human atrial samples [39].

Another important feature of the terminal crest is that it is an anisotropic region, as there is difference in the directions of the gap junctions; thus, it leads to an impaired conduction of the pulse in the transverse direction, while the longitudinal conductivity remains normal [40]. Anisotropy of cardiac tissue presents in different ways depending on the rate of excitation from the direction, and is determined by the direction of cardiomyocytes, while anisotropic conduction increases in pathological conditions, which is a risk factor of cardiac arrhythmias [41].

Thus, the area of the junction of the pectinate muscles and the terminal crest is potentially arrhythmogenic area; moreover, there is also a paranodal area, the functional significance of which both under normal conditions and in pathological conditions requires further examination.

PECTINATE MUSCLES AS A SUBSTRATE AND TRIGGER OF AF

There are quite a lot of studies in the literature where, using electrophysiological mapping methods, it has been proven that pectinate muscles can create a "re-entry" of excitation in the atria, which leads to the AF [42, 43]. Thus, in a study conducted on isolated samples of atrial tissues of dogs, it was determined that large pectinate muscles form the morphological basis for initiating the re-entry of excitation in the atria and prolong the lifetime of waves of re-entry excitation (anchoring), which can lead to fibrillation activity [9]. In another study on human atrial samples, authors concluded that the created surface heterogeneity due to pectinate muscles creates electroanatomic substrates for the re-entry of excitation. However, in this study it was also revealed that in the regions of the atrium exposed to fibrillation, an increase in the percentage of fibrosis in the pectinate muscles can be noted [44].

In general, many researchers associate the ability of the pectinate muscles to create a re-entry of excitation with thickening of the atrial tissue in this area and the complex branching structure of the pectinate muscles, which leads to the occurrence of preferred ways of rapid excitation along the pectinate muscles associated with the terminal crest [45, 46].

In the available literature, we also found information about the automatism of pectinate muscles. For example, Z.G. Guo et al. (1983) in their study isolated pectinate muscles from the right auricle of the human atrium to study their physiological properties. For

comparison, muscle samples were taken from the human right atrium. This study demonstrated that isolated samples of pectinate muscles can contract and have an automatism and, also, they develop a stable large amplitude of contractions with a smaller size compared to atrial samples, which can be associated with a coherent arrangement of muscle fibers and a relatively larger surface area [47]. However, the cause of the automatism of the pectinate muscles remains unclear, since there is no data in the literature on the presence of cardiomyocytes generating excitation. We consider this property to be pathological, since there is no data on the presence of special cells and ion channels for generating excitation under normal conditions. This region is characterized by the absence of expression of the hcn4 ion channel (Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4), which is necessary for the generation of excitation in cardiac pacemakers [48]. However, it has been proven that the expression of hcn4 outside the pacemakers in the right auricle of the atrium, where the pectinate muscles are located, increases with age, but expression increases even more in patients with AF, compared with healthy population [49]. In other words, the detected properties of automatism in the pectinate muscles can be a source of ectopic stimulation, which in turn initiates AF. However, there are very few studies confirming the possibility of pectinate muscles to show automatism in the available literature, which determines the need for further research.

POTENTIAL CLINICAL SIGNIFICANCE

Recently, based on the use of the so-called "upstream therapy", numerous attempts have been made to slow or stop the progression of AF by affecting the underlying cardiovascular disease and the natural course of the arrhythmia itself. However, progress in this area has been limited. The detection of electroanatomic substrates and ectopic activity zones outside the orifices of the pulmonary veins in the atria and pectinate muscles may explain the low efficiency of the ablation of the orifices of the pulmonary veins in patients with persistent AF. Further studies of the morphofunctional significance of the pectinate muscles and their interaction with the heart conduction system can reveal previously unknown associations in the pathogenesis of this disease, contribute to the correction of treatment strategy and improve treatment outcomes, protecting the patient not only from the effects of arrhythmia, but also from the progression of AF from the stage that is easily treatable to a condition refractory to therapy.

CONCLUSION

In conclusion, one of the main features of the pectinate muscles is the ability to quickly conduct excitation, providing synchronous regulation of atrial contractile activity. This functional property plays a great role in the embryogenesis of the heart, since the development of pectinate muscles correlates with an increase in the excitation rate of the atria. This function is due to the presence of special proteins Cx 40, Cx 43, NaV1.5, which are also found in Purkinje fibers and are necessary for rapid excitation. Moreover, due to the complex architecture of the pectinate muscles, the re-entry of excitation and AF become more likely to occur. Nevertheless, several issues related to the automatism of the pectinate muscles and their interaction with other anatomical structures, which may be the initiating mechanism for the occurrence and development of AF, is still poorly investigated. To answer to these questions, further morphoanatomical and electroanatomic studies are required in order to improve the outcomes of treatment in this population.

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