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Research Article

HEART RHYTHM DISTURBANCES IN CONNECTIVE TISSUE DYSPLASIA

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ABSTRACT

The article discusses the association between connective tissue dysplasia (CTD) and arrhythmias, particularly focusing on mitral valve prolapse as a potential risk factor for life-threatening ventricular arrhythmias and sudden cardiac death. Various studies emphasize the structural and mechanical abnormalities in the heart that contribute to arrhythmogenic phenotypes in CTD patients, such as fibrosis, mitral annular disjunction, and accessory chordae. Additionally, the text explores the role of autoantibodies, cardiac remodeling, and autoimmune processes in mediating rhythm disturbances and cardiac complications in CTD. The importance of ECG analysis, neural networks, and stress tests in detecting and monitoring arrhythmias in CTD patients is highlighted. The research underscores the significance of understanding the morphological basis and pathophysiological mechanisms of arrhythmias in CTD patients to improve therapeutic strategies and enhance patient outcomes.

KEYWORDS

Connective tissue (CT), Connective tissue dysplasia (CTD), Mechanoelectric feedback (MEFE), heart rhythm disorders, mitral annular disjunction (MDA), sudden cardiac death (SCD), Stretch-activated channels (SACs).

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INTRODUCTION

Arrhythmias in connective tissue dysplasia can range from harmless to life-threatening, and the study of this aspect of CDT is of interest to researchers. Considering that the incidence of connective tissue dysplasia, according to the latest data, Shodikulova G.Z., Mirzaev O.V., (2020) in the Uzbek population is about 9%, arrhythmic syndrome with this pathology can be a serious problem for cardiologists and therapists in our country.

In case of CTD, the following studies and opinions explain the relatively high risks of developing arrhythmias and the substrate for their formation.

Mechanical effects on the myocardium of the left atrium and ventricle during mitral valve prolapse, which is a benign disease, may underlie the high risk of developing life-threatening ventricular arrhythmias and sudden cardiac death - this new specific phenotype can be identified as arrhythmogenic MVP. Malignant arrhythmias in MVP can occur multifactorially under the influence of abnormal components of the LV myocardium (fibrosis, scars) and a constant trigger - mechanical stretching. The presence of focal fibrosis in the inferolateral wall of the LV is arrhythmogenic, as is diffuse LV fibrosis, thickening of the mitral annulus and valve leaflets, elongation and an increased number of chords [9, 15].

A similar view is shared by Nagata Y et al (2023), suggesting that basal inferoposterior myocardial fibrosis in MVP is associated with abnormal mechanical effects on the myocardium, potentially associated with ventricular arrhythmia. These associations suggest pathophysiological links between mechanical abnormalities associated with MVP and myocardial fibrosis, which may also be associated with ventricular arrhythmia and are potential imaging markers of increased arrhythmia risk. It can be assumed that the degree of arrhythmogenicity of mitral valve prolapse may be associated with the severity of mitral regurgitation and LA hyperextension.

According to Cristina Basso et al. (2019), the origin of malignant arrhythmias in MVP is likely determined by a combination of substrate (regional hypertrophy, myocardial fibrosis and the presence of Purkinje fibers) and trigger (mechanical stretch) due to primary morphofunctional abnormalities of the mitral annulus.

According to Chakrabarti AK et al. (2022), mitral valve prolapses (MVP), a common valvular heart disease despite a largely benign course, is increasingly recognized as a representative of the arrhythmic phenotype, correlated with ventricular arrhythmias and sudden cardiac death (SCD). Pathophysiological mechanisms associated with arrhythmias include cardiac fibrosis, changes in the ventricular refractory

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period caused by mechanical stress, and electrophysiological changes in Purkinje fibers.

Also, among the pathologies of the mitral valve in CTD, it is worth noting mitral annular disjunction (MDA), a condition of abnormal displacement of the mitral valve leaflet to the wall of the left atrium, which is often found in patients with MVP. According to Wu S and Siegel RJ (2022), MDA is associated with the risk of developing malignant ventricular arrhythmias and sudden cardiac death, so recognizing this diagnosis and risk stratification is very important. Considering the above, this anomaly can also be associated with CTD, which indirectly confirms the presence of a connection between arrhythmias and the underlying pathology [14].

An interesting work by Tison GH et al., (2023), involves the use of a convolutional neural network in the analysis of a 12-lead ECG. As a result, the neural network made it possible to identify MVP with a risk of ventricular arrhythmias, death and/or fibrosis and to identify new ECG correlates of arrhythmia risk. According to the authors, this ECG-based neural network can help select patients with MVP who need more careful monitoring and/or SM-ECG.

Velthuis S et al. (2021) believe that tension on the LV wall by accessory chordae and tendinous filaments can serve as a trigger for ventricular arrhythmias of the heart, participating in electrocardiographic conduction and, theoretically, being a source of ventricular arrhythmias.

According to some studies, additional chords in the left ventricle can provoke the development of ventricular extrasystoles, and the likelihood of developing extrasystoles depended on the shape of the chords [17].

Recently, studies have appeared to confirm the effect of cardiac remodeling in supraventricular cardiac arrhythmias. Mechanoelectric feedback (MEFE) in the heart operates through several mechanisms that serve to regulate cardiac function. Stretch-activated channels (SACs) in the myocyte membrane open in response to cell elongation, and tension generation depends on stretch, shortening rate, and calcium concentration [8, 9]. MEFE is an important aspect of cardiac function and has the potential to mitigate activation problems [10]. It is likely that SACs, when using electrocardiogram and volume-time curves, may show that each of their patterns has different effects on the cardiac pattern. In addition, the obtained models of stretch-activated channels on the membranes of cardiomyocytes confirmed the role of MEFE in the occurrence of fibrillation and defibrillation in the absence of structural damage to the heart [11]. Non-selective stretch-activated channels, as an additional mechanism of MEFE, contribute to the deployment of heterogeneous diastolic transmembrane voltage, more pronounced

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contraction and delayed repolarization in highly stretched parts of the atria. The differential and combined effects of these three MEFE mechanisms during activation of sinus rhythm in a four-chamber human heart model may have implications in arrhythmogenesis, both in terms of substrate (repolarization gradients) and triggers (ectopia) [12].

Myxomatous degeneration, being one of the signs of CTD, can mediate rhythm disturbances, for example, provoke bundle branch blocks. When this formation is localized on the septal cusp of the tricuspid valve, there is a high probability of blockade of the right bundle branch [3, 4].

ECG serves as an important tool in searching for the causes and understanding the process of the formation of cardiac arrhythmias. This method is also effective in patients with CTD. In patients with CTD, prolongation of the QT interval may be associated with MVP and the arrhythmogenic effect of catecholamines, which are produced more actively compared to individuals without CTD [3, 4, 5]. The coexistence of long QT syndrome and arrhythmogenic biflaflete MVP syndrome can lead to a rare but malignant clinical presentation characterized by potentially life-threatening arrhythmias, despite maximal therapy for long QT interval [16].

The QT interval varies depending on the type of MAS in patients with CTD. For example, with MVP, as mentioned above, the Q-T interval is lengthened, and in 1/3 of patients with abnormally located muscle bands of the LV, it is shortened.

According to Shodikulova G.Z. et al (2022), [9] a decrease in the level of Mg+2 and an increase in titers of autoantibodies to type I collagen are interconnected, and the dynamics of changes in the level of antibodies, as well as the level of magnesium, depending on the severity of the clinical course, can serve as a method for assessing the progression of the pathological process and the prognosis of the disease , i.e. autoantibodies, as a pathogenetic factor, have a place.

Autoantibodies are capable of exerting a whole range of effects that affect the conductivity of the heart, namely, initiating cell division, vascular constriction, and indirectly reducing the ability of the myocardium to contract, provoking necrosis of cardiac muscle cells [10]. There are studies indicating a relationship between the degree of autoimmune processes in the myocardium and the depth of morphological changes in the heart [11].

Autoimmune diseases are diseases that cause damage to the body's tissues as a result of immune dysfunction, often affecting several organs and systems. The heart is one of the common target organs of autoimmune diseases. Subsequently, immune dysfunction with cardiac damage develops microcirculatory disorders,

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arrhythmias, pericardial damage, myocarditis, myocardial fibrosis and valvular dysfunction [12].

The most important factors underlying rhythm disturbances are inflammation and fibrosis of the myocardium. Inflammatory processes and oxidative stress lead to necrosis of cardiomyocytes followed by electrical and structural remodeling. In addition, chronic inflammation is the pathophysiological basis linking autoimmune processes to autonomic dysfunction, including excessive sympathetic activation and decreased parasympathetic function. Autoantibody-mediated inhibitory effects on cellular events (eg, L-type potassium or calcium currents, cholinergic or β1-adrenergic M2muscarinic receptor signaling) can also lead to cardiac arrhythmias. Drug-induced arrhythmias caused, for example, by corticosteroids, methotrexate, chloroquine, are also observed in patients with autoimmune processes [13].

One of the hypotheses explaining the development of cardiac complications in DST is an imbalance of the autonomic system, which mediates disruption of the functional activity of the SA node through the inclusion of supra- and ventricular centers of impulse production.

According to Herring, N. (2019), cardiac autonomic control is most promising for clinical use in achieving long-term success in the treatment of arrhythmias. In their opinion, many primary cardiovascular diseases, such as hypertension, acute myocardial infarction and heart failure, are also diseases of the autonomic nervous system. Sympathetic hyperactivity and vagal insufficiency are powerful negative predictors of morbidity and mortality associated with arrhythmias and sudden cardiac death, and neuromodulation therapy may be clinically important in the treatment and prevention of fatal arrhythmias [14].

There are also studies confirming the existence of a connection between mechanical and autonomic modulation of heart rate. Stretching the walls of the heart chamber causes both an increase in heart rate and a decrease in the response to stimulation of the vagus nerve in some animals. Conversely, when heart rate is decreased by vagus nerve stimulation, the stretch-induced increase in heart rate is enhanced. The stretch response is similarly enhanced when heart rate is first decreased by pharmacological parasympathetic or cholinergic stimulation and decreased when the heart rate is increased by adrenergic stimulation. However, whether these changes in the chronotropic response to stretch are due to the interaction of mechanical (stretch) and autonomic (sympathetic, parasympathetic components) components or are simply the result of HR-dependent differences in the electrophysiological response to stretch is difficult to say [several studies have reported that positive chronotropic the response to stretch increases with a

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decrease in heart rate, regardless of the nature of the decrease in heart rate [15].

Physical and psycho-emotional stress tests are one of the important methods for diagnosing heart rhythm disturbances. These tests promote the release of neurotransmitters - norepinephrine, dopamine and hormones - adrenaline, and noradrenaline into the blood, activate the sympathetic segment of the autonomic nervous regulation, increasing the likelihood of arrhythmias. A number emphasize the importance of stress tests in arrhythmias [17, 18, 19], and provide information confirming the presence of certain rhythm disturbances in almost half of the healthy people after stress tests and in a sample of patients with morphological changes in the heart (84-86 %).

CONCLUSION

Thus, studying the cardiovascular system in patients with DST, in particular rhythm disturbances, determining their morphological basis, and understanding the mechanisms of initiation and progression of arrhythmias, will allow a deeper understanding of the problem of cardiovascular complications, and drawing up further tactics for managing patients based on the data obtained will create the opportunity to improve approaches to therapy patients with arrhythmic syndrome against the background of DST, improving their quality of life and prognosis of their existing cardiovascular diseases.

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