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Arrhythmias and autonomic nervous system dysfunction in acute and chronic diseases with right ventricle involvement

Zaburzenia rytmu i funkcji układu autonomicznego w przebiegu ostrych i przewlekłych chorób z zajęciem prawej komory serca

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Abstract

The right and left hearts differ from one another in their anatomy and function. This disparity demonstrates itself in different heart muscle compositions, arrangements of cardiac conduction system elements, and distributions of autonomic nervous system receptors. These differences mean that diseases that mainly affect the right heart, such as acute pulmonary embolism, chronic pulmonary hypertension, right ventricular infarction or arrhythmogenic right ventricular cardiomyopathy, as well as some congenital heart diseases and connective tissue diseases, have a distinct clinical course and potential complications. This leads to an increased incidence of cardiac rhythm disturbances in this group, with distinctive types of arrhythmia specific for every disease. In order to help clinicians select the best diagnostic and therapeutic methods, we here summarise current knowledge about arrhythmic complications and cardiac autonomic nervous system functions in diseases with right heart involvement.

Key words: arrhythmias, cardiac autonomic nervous system, acute pulmonary embolism, pulmonary hypertension, right ventricular involvement

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Introduction

The right and left ventricles differ in their anatomy and function, which is reflected in the different structure of the myocardium, different composition of the conductive system, and different distribution of autonomic nervous system receptors. Taking into account the wide spectrum of acute and chronic diseases mainly involving the right ventricle, the following review summarises current knowledge about cardiac arrhythmias and the function of the autonomic nervous system in diseases such as acute pulmonary embolism (APE), chronic pulmonary hypertension (PH), right ventricular infarction (RVI), arrhythmogenic right ventricular cardiomyopathy (ARVC), as well as congenital heart defects and connective tissue diseases with dominant right ventricular involvement.

In clinical practice we have several non-invasive or minimally invasive methods to assess the functions of the autonomic nervous system, of which the most commonly used are: assessment of heart rate variability (HRV), measurement of heart rate turbulence (HRT), assessment of arterial baroreceptor activity, and the orthostatic or tilt test.

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A detailed discussion of these methods and their importance in everyday practice, especially in predicting the risk of arrhythmic events, is available in medical publications [1, 2]. Today there is no doubt about the importance of inadequately increased sympathetic activity in promoting the occurrence of arrhythmia. Although the assessment of autonomic system function has traditionally been used mainly in patients after myocardial infarction or chronic heart failure with impaired left ventricular systolic function (especially by using HRV and HRT) [1, 2], there is more and more data regarding their potential use in diseases with dominant right ventricular involvement, as discussed in the following article.

Acute pulmonary embolism

Venous thromboembolism (VTE) is the third most common cardiovascular disease. Its most dangerous clinical manifestation is APE, the main cause of hospitalisation, morbidity and mortality in Europe. In the management of a patient with newly diagnosed APE, all too often not enough attention is given to the potential occurrence of various arrhythmias and their prognostic significance, and even more rarely to the possible dysregulation of the autonomic system resulting in abnormal cardiovascular reactions. However, the clinical course of APE with acute right heart pressure overload is often complicated by cardiac arrhythmias. Arrhythmia may additionally be favoured by myocardial ischaemia and blood hypoxemia [3].

Supraventricular arrhythmias

A significantly increased risk of atrial fibrillation (AF) in the course of APE has been demonstrated by Australian researchers. The incidence of AF in a group of 1,142 patients with APE was as much as 13%, and the risk of this arrhythmia was more than nine times higher compared to the age-adjusted general population. Moreover, it was shown that patients with APE and atrial fibrillation had more comorbidities. Independent risk factors for this arrhythmia included age ($p < 0.001$), history of congestive heart failure ($p = 0.02$), diabetes ($p = 0.02$), and obstructive sleep apnoea ($p = 0.009$) [4].

The occurrence of atrial fibrillation (*de novo*, persistent or chronic) in the course of APE may also result in a non-optimal initial assessment during the diagnostic process when this disease is suspected. Although the reported frequency of tachycardia on the first day in APE is 24–39%, no detailed data is available on the incidence of atrial fibrillation in these statistics [3]. One study indicated that patients with supraventricular tachyarrhythmias are more often assigned to the high probability group of venous thromboembolism based on a modified Geneva scale ($p = 0.04$), and this group also scored higher on the simplified Pulmonary Embolism Severity Index (sPESI) scale ($p < 0.001$), which could be attributed to scoring additional points for tachycardia > 110/min. [5]. Another noteworthy observation arising from this study is the fact that in patients with paroxysmal AF (compared to patients with sustained arrhythmia or sinus rhythm), indirect echocardiographic features of right ventricular congestion were observed more frequently, *i.e.* increased calculated pressure in the pulmonary trunk ($p = 0.01$) or reduced acceleration time through the pulmonary valve ($p = 0.04$). However, in this study no significant relationship was found between atrial fibrillation and in-hospital mortality ($p = 0.067$), and therefore the question regarding the impact of this arrhythmia on the risk of APE patients' death remains unresolved [5].

The relationship between APE and the occurrence of supraventricular arrhythmia is also highlighted by the analysis of Hayiroğlu et al. [6], which describes the relationship between the occurrence of specific arrhythmias depending on thrombolytic therapy usage or the lack of it. In this study, using non-invasive treatment resulted in significantly more frequent different atrial arrhythmias ($p < 0.001$), despite the lack of clear differences in the structure and volume of the atria between the assessed groups [6]. The further analysis of the obtained results is ambiguous, because patients who required thrombolytic treatment had worse clinical status at the baseline (and supraventricular arrhythmias presented less often). In addition, no differences in the incidence of ventricular arrhythmias were observed between the assessed groups. On the other hand, the dissolving of thrombi during fibrinolytic therapy not only improves cardiovascular and respiratory function, but also reduces the thrombus load and, consequently, the release of proinflammatory cytokines from them, which are also seen as potential factors that increase the occurrence of various arrhythmias [6].

Ventricular arrhythmias

Currently, there is no detailed data on the occurrence, clinical course or implications of ventricular arrhythmias in the course of APE.

Prognostic value

It is worth noting that the occurrence or severity of cardiac arrhythmias [as well as other electrocardiographic (ECG) abnormalities] may also be the first manifestation of the onset of clinical worsening in the course of APE: unexplained bradycardia, seemingly inadequate tachycardia with episodes of tachyarrhythmia, as well as the occurrence of intraventricular conduction disorders indicate a developing shock, most commonly just after a progressive reduction of blood pressure. The significance of specific abnormalities in standard 12-lead ECGs indicating adverse in-hospital and long-term prognosis in patients with APE have been discussed in detail in other studies [7].

Syncope and its association with cardiac arrhythmias

According to data from various studies, fainting and syncope in patients with APE are observed in up to 10% of cases, and adverse effects of these events on the prognosis have been proven [8]. It seems that the fainting and syncope are usually reflexive, but it cannot be excluded that short-term haemodynamic instability is the result of brady- or tachyarrhythmia. It has been shown that syncope in the course of APE is more common in people with pre-existing left bundle branch block (LBBB) and in patients with fresh right bundle branch block (RBBB) (high probability of short-term bradyarrhythmia) [9].

Autonomic heart system

The risk of bradyarrhythmia in the course of APE, overlooked in risk stratification, is also partly justified in the aspect of the autonomic regulation of the cardiovascular system disorders in the course of APE. In healthy pulmonary arteries, the vascular tone is low, which means that at rest they are maximally expanded. The pulmonary circulation vessels are equipped with noradrenergic receptors with variable densities depending on the dimensions of individual arterioles, and are not present in vessels < 700 μm in diameter. Stimulation of the sympathetic nervous system has been found to have a different effect depending on whether the pulmonary arteries have normal or elevated pressure. In the course of acute pulmonary hypertension (PH), adrenaline has a vasodilating effect on vessels equipped with receptors that capture it, and this vasodilatory effect, in addition to vasoconstriction, is caused by noradrenaline and epinephrine. Ultimately, activation of the sympathetic nervous system under PH conditions results in vasoconstriction followed by vasodilation. In addition, sympathetic stimulation increases the tone of the pulmonary venous system, which further increases the pressure in the arterial system and intensifies the mechanisms discussed above [10]. It has been observed that the severity of the sympathetic nervous system activity, as well as the renin–angiotensin–aldosterone axis, is also affected by the load and distribution of thrombi and the duration of vascular occlusion. It is also suspected that in neurohormonal disorders Bezold-Jarish reflexes play an important role, and the apnoeas, bradycardia and hypotension caused in their course may additionally contribute to the complicated clinical course [10].

There is no doubt, therefore, that in patients with APE, the severity of autonomic disorders may have a significant impact on the course of the disease, including the occurrence of specific arrhythmias or the occurrence of fainting and syncope. It is therefore surprising that there have been no studies that would non-invasively assess the function of the autonomic heart system in patients with APE, for example using HRV or HRT.

Treatment

It should also be remembered that due to a lack of specific recommendations for the treatment of cardiac arrhythmias complicating APE, antiarrhythmic regimens appropriate for the general population are used, and that causative therapy is of paramount importance in such a situation [3].

Pulmonary hypertension

Pulmonary hypertension is diagnosed if the mean pulmonary artery pressure is ≥ 25 mm Hg when measured by direct invasive methods during right heart catheterisation [11]. Pulmonary hypertension can be a primary disease, or secondary to other diseases including pulmonary thromboembolism after APE (so-called chronic thromboembolic PH). Chronic PH is associated with progressive heart failure, and as a consequence autonomic dysfunction which could cause dysregulation of beta-adrenergic receptors in the myocardium, among others. Complex mechanisms of organic damage and functional dysfunction, typical of heart failure, may result in various cardiac arrhythmias in these patients. As in the case of acute PH in APE, issues related to arrhythmias in patients with chronic PH are insufficiently understood among practitioners.

Supraventricular arrhythmias

The results of available studies indicate that various types of supraventricular arrhythmias are observed relatively frequently in the course of PH. In one study, conducted on a population of 231 people with arterial PH, the cumulative risk of significant arrhythmias was 11.7%, and the annual risk was 2.8% per patient. The presence of arrhythmias was associated with a worse prognosis. In the population assessed in this study, the most common arrhythmias were atrial flutter (AFL) (in 6.5%), atrial fibrillation (AF) (in 5.6%), and recurrent tachycardia in the atrioventricular (AV) node (in 1.3%) [12]. Significantly, in people with PH and AF, deaths were much more frequent (in up to 82% of cases!) when compared to patients in whom sinus rhythm was restored (in 6.3% of cases) [12]. Olsson et al. [13] found at least one *de novo* AFL or AF episode in 25% of people in another study conducted prospectively over five years on a group of 239 PH patients. In addition, both supraventricular arrhythmias occurred at a similar frequency, and their presence was associated with a significant worsening of the clinical condition (in 80%) and worsening of heart failure (in 30% of patients). In addition, it was demonstrated that unmeasured AF resulted in a significant increase in the risk of death in this group ($p = 0.01$) [13]. In a systematic review, Handoko et al. [14] reported a significantly lower incidence of supraventricular arrhythmias in patients with PH, *i.e.* about 3% per year, confirming the adverse prognostic value of persistent atrial fibrillation.

Ventricular arrhythmias

The available data on ventricular arrhythmias in chronic PH is very limited. Although the review by Handoko et al. [14] cited above reports the estimated risk of death from ventricular arrhythmias in patients with PH to be 8–26%, a full assessment of the incidence and impact of ventricular arrhythmias on the clinical course and prognosis in patients with PH requires further studies.

In one of the few studies, Witte et al. [15] among a group of 64 participants with PH found more than twice as many extrasystoles compared to the control group ($p < 0.01$), as well as observed an increased risk of malignant ventricular arrhythmias in this population. In our Holter assessment of 22 patients with arterial and 11 patients with thromboembolic PH, we found non-sustained ventricular tachycardia occurrence in these patients to be 13.6% and 27.3%, respectively ($p = 0.63$) [16].

Autonomic heart system

More and more data indicates a significant dysregulation of the cardiac autonomic system in people with PH, regardless of its cause and regardless of the age of the patient [17]. These patients show significantly worse HRV and HRT parameters, indicating chronic overstimulation of the sympathetic nervous system. Study from our centre has also shown that people with PH and abnormal HRT are characterised by a significant deterioration of various functional, biochemical and haemodynamic parameters, such as: 6-minute walk test distance ($p = 0.05$), resting saturation ($p = 0.05$), post-exercise desaturation ($p = 0.03$), or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ($p = 0.02$) [18]. These results indicate that there is a clear relationship between the stage of PH and the function of the autonomic system. This means that the easily interpretable HRT result is potentially useful in predicting the increased risk of clinical deterioration, and possibly also death. Interestingly, during the continuation of previous research in our centre, it was shown that the severity of Holter dysfunction assessed by the Holter method is potentially greater in the case of thromboembolic aetiology than arterial PH and in more advanced clinical forms [World Health Organisation (WHO) classes 3 and 4 vs. 1 and 2] [16]. The results published by Witte et al. [15] stand in opposition to the above observations, which confirmed a decrease of HRV in arterial PH, but not in the case of thromboembolism. A potential explanation for the differences observed between the studies is a different selection of study groups. Given the current state of knowledge, possible differences in the functions of the autonomic system and their importance in the course of arterial and thromboembolic PH require further evaluation.

An interesting comparative analysis was also carried out in the Łódź centre, observing a greater risk of death from cardiovascular causes associated with an increase in the number of late ventricular potentials in the group of patients with arterial PH compared to those with heart failure in the course of left ventricular dysfunction ($p = 0.024$). In both groups, the WHO functional class distribution was similar, and no statistical differences were found for most of the assessed HRV parameters. The prognostic implications of these irregularities require further observation [19].

Right ventricular heart failure

As mentioned earlier, the onset or worsening of cardiac arrhythmias in PH patients actually accelerates the onset of heart failure [20]. Atrial fibrillation is the most common arrhythmia in the group with right ventricular heart failure (RVHF). It is estimated that it occurs in up to 50% of patients, with an increasing frequency depending on a larger functional class [20]. Ventricular arrhythmias are also common, especially in those who also have a left ventricular ejection fraction. Myocardial damage and increased fibrosis provide the substrate for reentry loops, and this mechanism is considered to be responsible for most malignant and potentially malignant ventricular arrhythmias.

Treatment

The treatment of supraventricular arrhythmias in chronic PH does not differ significantly from the treatment of cardiac arrhythmias in other clinical situations. For AF, AFL and tachycardia, electrical cardioversion and ablation of arrhythmia are used. Pharmacotherapy includes the use of beta-blockers, non-dihydropyridine calcium antagonists, digoxin and amiodarone [12]. The negative inotropic effect of the first two of these drug groups may be undesirable in patients with high right ventricular afterload, therefore their use must be preceded by a risk and benefit evaluation and they must undergo regular clinical monitoring. It is worth remembering that the use of amiodarone in patients with primary PH is associated with a much more frequent occurrence of thyroid dysfunction compared to the general population (19–24% vs. 2.5–9.5%) [21]. Amiodarone may also have side effects affecting the respiratory system, which includes the development of pulmonary fibrosis, and thus a further increase in pulmonary artery pressure [22].

Right ventricle infarct

Right ventricular infarction usually coexists with acute myocardial infarction with ST-segment elevation of the left ventricular wall, which occurs in 30–50% of cases. The term 'right ventricular infarction' is, in fact, an imprecise term because, in addition to conditions with typical necrosis, in some cases, acute ischaemic right ventricular dysfunction resulting in a diagnosis or RVI is mostly related to a viable myocardium [23, 24].

Prognostic value

An assessment in the early 1990s showed that RVI was an independent factor in the development of serious complications, including cardiogenic shock, ventricular fibrillation, third-degree AV, and the need for temporary stimulation. Moreover, the right ventricular infarction resulted in increased in-hospital mortality, from 5% to 31% ($p < 0.001$), and an increased serious complication rate, from 28% to 64% ($p < 0.001$) [25]. In addition to the increased risk of early peri-infarct complications, RVI also results in an increased risk of long-term mortality. The group most affected by unfavorable prognosis comprises patients with RVI without improvement of right ventricular haemodynamic function and with accompanying PH, as demonstrated during an eight-year follow-up by Shahar et al. [26].

Bradyarrhythmias

In a recently published study by Kumar et al. [24], co-existing RVI was found in 32.9% of 573 patients from an Indian population with an inferior heart wall infarction treated with thrombolysis. Importantly, cardiogenic shock (22.2 vs. 1.8%) and death (14.3 vs. 2.34%) were significantly more frequent in the subgroup of patients with RVI. Patients with concomitant RVI also had a higher incidence of total AV block (30.2 vs. 16.4%), while second-degree AV block (4.8 vs. 11.7%) was less frequently observed. The presence of AV blocks (especially total) also resulted in a significantly more frequent occurrence of peri-infarction deaths ($p < 0.03$) [24]. The latest data suggests that in highly developed countries, where percutaneous coronary intervention is commonly used in the treatment of acute coronary syndromes, the incidence of clinically significant AV blocks has decreased to approximately 3% and usually resolves spontaneously within 2–7 days. AV blocks of a longer duration may require prolonged, or even permanent, cardiac electrostimulation, and this occurs in approximately 9% of cases. Patients with myocardial infarction irrespective of its location complicated by AV block are at higher risk of in-hospital death and over the course of a 30-day follow-up. However, the presence of AV conduction disorders does not affect the long-term prognosis, defined as death within > 30 days post-myocardial infarction. Indications for permanent AV stimulation are persisting total AV block (especially in co-existence of RVI), and haemodynamic instability [27].

Patients with prolonged ischaemia and long-term chest pain, in whom coronary revascularisation was incomplete, as well as patients with pre-existing arrhythmia substrate, bear the highest risk of potentially serious arrhythmias during myocardial infarction [28]. It is worth remembering that most arrhythmias appear in the first hours of myocardial infarction and disappear after successful invasive treatment, and so reperfusion therapy should be sought as soon as possible.

Sinus bradycardia

A common complication in the course of RVI is sinus bradycardia, which usually does not require special treatment (although atropine should be used if it causes hypotension). It has been proved that the presence of sinus bradycardia (without AV block) and hypotension increase the risk of cardiodepressive reflex activations from the cardiac vagus branches located in the inferior wall and right ventricle (Bezold-Jarish reflexes) [29]. Furthermore, it has been found that acute myocardial infarction induces morphological and phenotypic changes in the intracardiac components of the autonomic system, incorrectly reducing the neuron's potential in response to specific stimuli [30].

Autonomic system

There is an extensive evidence that in patients with acute myocardial infarction, excessive activity of the sympathetic nervous system results in an increased risk of cardiovascular events, including sudden cardiac deaths caused by arrhythmia. The protective effect of the parasympathetic nervous system in these patients has also been demonstrated. In recent years, a great number of studies have been conducted involving large groups of patients that have proven the influence of the autonomic heart system on prognosis after myocardial infarction. Most often, non-invasive measurement of heart rate variability and turbulence is used to assess the function of the parasympathetic balance (reduced HRV and HRT parameters indicate increased risk) [31]. To date however, no extensive and significance-oriented studies focused on imbalances in the autonomic system have been conducted to assess the course and prognosis of patients with concomitant RVI.

Treatment

Treatment of cardiac arrhythmias in RVI does not deviate from the standard management of peri-infarct arrhythmias. Detailed procedures are included in the current guidelines of scientific societies, including the European Society of Cardiology.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a congenital heart disease with autosomal dominant inheritance due to mutations in the genes encoding desmosomes or desmosome-associated proteins. In the course of ARVC, myocardial fibrous fat remodelling occurs, which is clinically manifested by the occurrence of cardiac arrhythmias (most often ventricular) and progressive impairment of the right

systolic function, and in some patients also the left ventricle [32]. Despite non-sex-chromosomal inheritance, clinical manifestations of ARVC are three times more common in men than in women. In addition, men are more likely to present symptomatic arrhythmias ($p < 0.01$). What is more, arrhythmias in males appear earlier and are more severe than those suffered by women [33, 34].

There are three phases of ARVC progression: 1) asymptomatic, during which patients do not experience symptoms of the disease, but may develop ventricular arrhythmias and sudden cardiac deaths; 2) the phase of electrical dysfunction of the heart, manifesting as symptomatic arrhythmias and morphological abnormalities within the right ventricle, not detected using traditional imaging methods; 3) end-stage, characterised by signs of heart failure and frequent ventricular arrhythmias in the form of unstable or sustained ventricular tachycardia. Regardless of the severity of ARVC, the possibility of sudden cardiac arrest in the course of this disease should be considered.

Fibrous-fat tissue replacing normal myocardium in patients with ARVC causes a delay in right ventricular activation. These changes are first observed within the free wall and outflow tract from the right ventricle, which promotes the formation of re-entry loops and contributes to the formation of ventricular arrhythmias with the morphology of the LBBB [35]. Ventricular tachycardias with typical morphology from the right ventricular outflow tract occur much less frequently in the course of ARVC [32].

Risk of ventricular arrhythmia

In their meta-analysis, Bosman et al. [36] observed that the main predictor of ventricular arrhythmias in this patient group is right ventricular dysfunction. The frequency of ventricular arrhythmias they observed in patients with ARVC was 3.7–10.6%, and was dependent on the study group and thus indirectly on the stage and genetic type of the underlying disease [36]. It is worth noting that in addition to the right ventricular function and morphology, a specific disease genotype is important during prognosis assessment. A multicentre study of 577 people with ARVC showed that the type of mutation and the number of mutations were important in the assessed population because it was shown (surprisingly) that those who had ventricular fibrillation and sudden cardiac deaths were younger than those who were only diagnosed with sustained ventricular tachycardia (median age 23 vs. 36 years, $p < 0.001$) [34].

Supraventricular arrhythmias

There are only a few reports regarding the occurrence of supraventricular arrhythmias in the course of ARVC. A recent study by Camm et al. [37] showed that significant supraventricular arrhythmias (especially atrial fibrillation) in ARVC occur in approximately 14% of patients. Factors associated with the occurrence of supraventricular arrhythmias in patients with ARVC were: male sex, older age, and enlargement of the left atrium [37].

Autonomic system

In recent years, it has been observed that ARVC is also associated with adrenergic system dysfunction, which is manifested by a decrease in noradrenaline and cyclic adenosine-3', 5'-monophosphatase in the myocardium. Decreased noradrenaline levels in the course of ARVC sometimes lead to abnormal stimulation of beta-adrenergic signalling pathways, and this can potentially result in increased myocardial fibrosis and increased arrhythmogenesis. Comparing endomyocardial biopsies of patients with ARVC to people with ventricular arrhythmia from the right ventricular outflow tract without structural heart disease, a significantly lower noradrenaline concentration was found in the ARVC group ($p < 0.04$), which indicates reduced activity of the sympathetic system in this group, and potential abnormalities in beta-adrenergic receptors function [38]. In another study, performed in patients with ARVC not taking antiarrhythmic drugs, significantly lower HRV values were observed, which reflected the sympathetic part of the cardiac autonomic system. A study by Paul et al. [39] also showed that 59% of patients with ARVC have sympathetic abnormalities independent of the genotype and degree of right ventricular dysfunction, and significantly increased risk of potentially life-threatening ventricular tachyarrhythmia ($p < 0.0005$). Studies using Holter's assessment of autonomic system function have also confirmed the dysfunction of this system in patients with ARVC, and that the decrease in HRV parameters is associated not only with a more frequent occurrence of ventricular arrhythmias ($p = 0.009$), but also with a lower ejection fraction in both the right and the left ventricle [40].

Treatment

Numerous sudden cardiac arrest episodes in the course of ARVC have led to the implantation of cardioverter-defibrillators becoming the first-line therapy in this group of patients. In one of the ARVC registers, as many as 108 out of 137, patients were implanted with a cardioverter-defibrillator. Analysis of intracardiac ECGs in these patients confirmed that the vast majority of observed ventricular arrhythmias were monomorphic. As mentioned above, this study also showed that the only statistically significant predictor of life-threatening tachyarrhythmias (sustained ventricular tachycardia ≥ 240/min. or ventricular fibrillation) was younger age at the time of ARVC diagnosis ($p = 0.036$). It has also been shown that antitachycardia pacing were the most effective form of therapy in this group of patients (in 92%), which indicates the importance of proper programming [41].

Congenital heart disorders

Any congenital heart disease can result in cardiac arrhythmias. In some cases, these arrhythmias can also be life-threatening. Among numerous congenital malformations with dominant right ventricular involvement and the frequent occurrence of cardiac arrhythmias, Ebstein's anomaly and Fallot's syndrome should be highlighted. Another disease, Eisenmenger syndrome (vascular lung disease) with the secondary development of irreversible pulmonary hypertension is the consequence of inadequately diagnosed and treated congenital defects with left-right leakage.

Ebstein's anomaly

Ebstein's anomaly is a rare disease, with an estimated frequency of about 5 per 100,000 live births. Although it is a congenital disease, it is often only diagnosed in adulthood. Ebstein's anomaly consists of an embryonic defect causing the tricuspid valve leaflets to move deeper into the right ventricle, which is accompanied by atrialisation and possible leakage at the level of the atria. Typical for this disorder is the presence of additional right-sided AV conduction pathways, resulting in a significantly higher number of arrhythmia episodes than in the general population. Atrioventricular recurrent tachycardia arising in the macro re-entry mechanism is sometimes poorly tolerated, manifesting in syncope in up to 30% of patients, and cases of its transition to ventricular fibrillation have been recorded [42]. In contrast, AFL or AF is most common in patients who are post-repair surgery (in 64% and 23% of patients, respectively) [43]. The incidence of AF increases with the age of the patient, resulting in up to a 100% increase in five-year mortality. On the other hand, sustained ventricular tachycardia relatively rarely appears spontaneously, although it can be induced during electrophysiological examination [42].

In one of the largest groups of patients with Ebstein's anomaly from one centre (143 patients of the Mayo Clinic), it was shown that significant arrhythmias occurred in 31% of cases before operative correction of the defect. The most common were supraventricular tachycardia not associated with additional pathways (17%), and Wolff Parkinson White syndrome (with supraventricular tachyarrhythmias, 10%, and without, also 10%). Other arrhythmias in Ebstein's anomaly, including atrial tachycardia, AFL as well as ventricular tachycardia and ventricular fibrillation, were rare (1% each) [44]. There is no report available on the function of the autonomic system in patients with Ebstein's anomaly and its impact on the development of cardiac arrhythmias.

Tetralogy of Fallot

Another congenital heart disease that needs to be discussed is tetralogy of Fallot, which involves the simultaneous occurrence of pulmonary stenosis, ventricular septal defect, overriding aorta, and secondary right ventricular hypertrophy. Tetralogy of Fallot occurs in up to 0.09% of live births. In previous studies, the risk of ventricular tachycardia among people with tetralogy of Fallot was estimated at 4–14% in 20–30-year follow-ups [45]. Sudden cardiac deaths in the course of ventricular tachyarrhythmias have long been considered the most common cause of mortality in this disease. This view was not confirmed however in a meta-analysis involving 39 studies with a total population of over 4,500 patients, where the risk of sudden death was determined to be 0.15% per year [46]. Interestingly, this risk does not increase linearly, but reaches its highest level 20–25 years after corrective surgery [47]. The incidence of supraventricular arrhythmias among patients affected by this syndrome is also high, due to numerous lesions in the heart structures altered by the defect and repair surgery. Over many years of observation, episodes of supraventricular tachycardia in the reentry mechanism have been observed in up to 30% of patients. Patients with tetralogy of Fallot also often have episodes of AFL and AF [48]. It is well-documented that complex disorders of the structure and function of the heart in patients with tetralogy of Fallot cause irregularities in the functioning of the autonomic system. Several studies have shown that significantly lower values of HRV time and frequency analysis parameters are observed in adults with corrected tetralogy of Fallot compared to healthy people. It is worth emphasising that these parameters improve along with the time elapsed since the procedure. Moreover, an inverse relationship has been found between the values of most HRV parameters and the duration of QRS complexes in ECG. This observation indicates that the greater the damage to the heart, the worse the function of the autonomic system, which may also translate into an increased risk of ventricular arrhythmias and sudden cardiac deaths in this group of patients [49].

Eisenmenger syndrome

Various types of cardiac arrhythmia are found in 15–20% of patients with vascular lung disease. In a study conducted on a population of 167 people with Eisenmenger syndrome, with a mean age of 38 ± 9 years, significant tachyarrhythmias were found in 28 patients. This was most often supraventricular tachycardia, AF or AFL, and unstable and sustained ventricular tachycardia. Interestingly, only 16% of the abovementioned study population received antiarrhythmic treatment. A trend towards an increased risk of death ($p = 0.07$) was observed among patients with known arrhythmia [50]. As in other patients with CPH, also the function of the autonomic heart system is disturbed in patients with Eisenmenger syndrome. In a study assessing HRV parameters in this group, significantly

lower values were observed both in time and in frequency analysis (compared to the control group of healthy people, p = 0.001) [51].

Treatment

The treatment of cardiac arrhythmias in patients with congenital malformations does not differ significantly from standard therapy, but amiodarone is preferred for ventricular tachyarrhythmias. However, invasive antiarrhythmic treatment should always be performed in an experienced centre. Despite the increased risk of arrhythmia in postoperative scar tissue, correction of the defect plays a key role in accordance with generally accepted standards.

Connective tissue diseases

Right ventricular involvement also occurs in the course of autoimmune connective tissue diseases. Cardiovascular involvement is most common in systemic sclerosis, lupus erythematosus, rheumatoid arthritis, polymyositis and dermatomyositis, as well as mixed connective tissue disease. In none of these diseases does selective right ventricular involvement occur, but possible development of PH in their course is often the cause of various arrhythmias and autonomic dysfunction. The risk of arrhythmia in this group of patients also results from progressive fibrosis, including the conduction system and variously intensified inflammation [52, 53].

Patients with **systemic sclerosis** are at the highest risk of various cardiac arrhythmias, both tachy- and bradyarrhythmia. The most common in people with this disease are numerous extrasystole beats, with a frequency of 25–75% reported in Holter analyses. Moreover, it has been shown that the occurrence of numerous ventricular extrasystoles is associated with an increase in the incidence of sudden cardiac deaths [52, 53]. Non-sustained supraventricular (approx. 50%) and ventricular tachycardia (in 7–13% of cases) are also very common in patients with systemic sclerosis. However, AF and AFL episodes are less frequent. In addition, AV conduction disorders, including 2nd and 3rd degree blocks, are also not uncommon in patients with systemic sclerosis [52, 53]. Analysis of HRV and HRT in patients with systemic sclerosis indicates a decrease in the activity of both components of the autonomic system of the heart, especially the parasympathetic part. An undoubted relationship between the deterioration of the autonomic cardiac system function and the development of PH in this group of patients has also been shown [54].

In the course of **lupus erythematosus**, the most frequently observed arrhythmia is inadequate sinus tachycardia. This occurs in up to 50% of patients and can be the only sign of heart involvement. Additionally, supraventricular extrasystoles are common, as well as short episodes of unstable supraventricular tachycardia (in approx. 30% of cases) and very rarely paroxysmal AF. However, ventricular arrhythmias and AV blocks in the population of people with systemic lupus erythematosus are uncommon. The reported frequency of additional ventricular beats is about 8%, while in the case of non-sustained ventricular tachycardia it is about 1% [53]. Among patients with systemic lupus erythematosus, as in people with systemic sclerosis, significantly lower HRV and HRT parameters have been observed, with a clear impairment of sympathetic heart tone, although parasympathetic tone is similar to that in healthy individuals [53].

In **rheumatoid arthritis**, in addition to other proarrhythmic factors characteristic of connective tissue diseases, the presence of rheumatoid nodules in the myocardium, infiltration of the conductive system and deposition of amyloid is typical. Cardiac involvement in this disease is usually asymptomatic, and arrhythmias appear relatively rarely [55].

Treatment

The therapy of arrhythmia and conductive disorders in people with connective tissue diseases does not differ significantly from the treatment appropriated for the general population. Knowledge of the underlying arrhythmias, and proper treatment of the underlying disease, remain particularly important in this group of patients.

Conclusions

Diseases involving the right heart have a distinct pathophysiology, clinical course, and potential complications. Typically, these diseases influence the function of autonomic nervous system, which leads to an increased potential for causing arrhythmias, with other types of arrhythmia being characteristic of particular disease entities (Table 1). It is important for clinicians to use this knowledge in practice, when treating patients with conditions listed in present study.

Table 1. Estimated incidence of various significant supraventricular and ventricular arrhythmias in various right ventricular involvement (data based on numerous references)

Arrhythmias	Acute pulmonary embolism [%]	Chronic pulmonary hypertension [%]	Arrhythmogenic right ventricular cardiomyopathy [%]	Ebstein's anomaly [%]	Tetralogy of Fallot [%]	Eisenmenger syndrome [%]	Systemic sclerosis [%]
AF	13	5.6	14**	No data (prior to correction) 23 (post correction)	No data	21	No data
AFL	No data	6.3		1 (64)	No data	< 7	No data
SVT	< 24–39*	> 1.3		17 (no data)	30	29	50
nsVT	No data	13.6–27.3	3.7–10.6	< 1 (no data)	4–14	21	7–13.5
sVT	No data	No data		1 (no data)		21	No data

*Including supraventricular tachycardia (SVT) with atrial fibrillation (AF) and atrial flutter (AFL); **mostly AF; nsVT — non-sustained ventricular tachycardia; sVT — sustained ventricular tachycardia; no data — no data available

Streszczenie

Prawa i lewa komora różnią się w swojej anatomii i funkcji, co ma swój wyraz w odmiennej budowie miokardium, zawartości elementów układu bodźcoprzewodzącego oraz dystrybucji receptorów autonomicznego układu nerwowego. Wymienione różnice sprawiają, że choroby przebiegające głównie z zajęciem prawych jam serca, takie jak: ostra zatorowość płucna, przewlekłe nadciśnienie płucne, zawał prawej komory serca czy arytmogenna kardiomiopatia prawokomorowa, a także wybrane wrodzone wady serca czy niektóre choroby układowe tkanki łącznej, odróżniają się na tle innych schorzeń swoją patofizjologią, przebiegiem klinicznym oraz potencjalnymi komplikacjami. Prowadzi to również do zwiększonej częstości wywoływania zaburzeń rytmu serca, przy czym dla poszczególnych jednostek charakterystyczne są inne rodzaje arytmii. W celu ułatwienia klinicystom wyboru metod diagnostycznych i leczniczych w poniższym opracowaniu zebrano aktualną wiedzę na temat zaburzeń rytmu oraz funkcji autonomicznego układu nerwowego serca w schorzeniach przebiegających z zajęciem prawej komory.

Słowa kluczowe: zaburzenia rytmu serca, układ autonomiczny serca, ostra zatorowość płucna, nadciśnienie płucne, zajęcie prawej komory serca

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