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Atrial fibrillation – etiology and pathogenesis

Etiologia i patogeneza migotania przedsionków

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Key words
atrial fibrillation, atrial flutter, etiology, mechanisms, microRNA, oxidative stress

Słowa kluczowe
migotanie przedsionków, trzepotanie przedsionków, etiologia, mechanizmy, mikroRNA, stres oksydacyjny

S u m m a r y

Etiology and pathomechanisms of atrial fibrillation and atrial flutter are complicated and the knowledge about them still remains incomplete. This may be the reason why currently applied methods of prevention as well as treatment remain unsatisfied. A number of clinical situations were identified that may conduce to occurrence of atrial fibrillation and atrial flutter and also lead to chronic forms of arrhythmia. Oxidative stress, enlargement/extension of atrium, cardiomyocytes overloaded by calcium ions, microRNA, inflammative factors and miofibroblasts' activation seem to be most engaged in process leading to atrial remodelling. Complete recognition of relationships between individual mechanisms may possibly enable to form new goals for prevention and therapy of atrial fibrillation and atrial flutter which may lead to better health and better quality of life in patients affected with the discussed heart arrhythmia. The paper presents the revision of current knowledge concerning etiology and pathophysiology of the above arrhythmia as well as explains relationships and interactions among particular mechanisms.

S t r e s z c z e n i e

Migotanie i trzepotanie przedsionków są wciąż istotnym problemem klinicznym, społecznym i ekonomicznym w dzisiejszym systemie opieki zdrowotnej. Wiedza o ich etiologii i patogenezie pozostaje wciąż niepełna. Może to w pewien sposób tłumaczyć brak pełnej skuteczności obecnie stosowanych metod zapobiegania napadom tych arytmii, jak również wciąż niezadowalającą skuteczność leczenia. Poszukiwania czynników etiologicznych oraz prace nad mechanizmami prowadzącymi do epizodów migotania i trzepotania przedsionków pozwoliły zidentyfikować pewne stany kliniczne mogące sprzyjać pojawianiu się napadów arytmii, jak również prowadzić do przejścia ich w postać przewlekłą. Stres oksydacyjny, powiększenie i/lub rozciągnięcie przedsionków, przeładowanie kardiomiocytów jonami wapnia, mikro RNA, czynniki zapalne oraz aktywacja miofibroblastów wydają się być zaangażowane w procesy prowadzące do remodelingu przedsionków. Jedynie pełne poznanie związków zachodzących pomiędzy poszczególnymi mechanizmami może doprowadzić do stworzenia nowego celu prewencji i terapii migotania i trzepotania przedsionków oraz umożliwić skuteczniejsze kontrolowanie omawianych arytmii, a w konsekwencji znacząco poprawić jakość życia i sytuację zdrowotna pacjentów, których problem ten dotyczy. W niniejszej pracy przedstawiono najnowsze dane z zakresu etiologii i patofizjologii migotania i trzepotania przedsionków, jak również omówiono wzajemne zależności poszczególnych patomechanizmów.

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INTRODUCTION

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common arrhythmias in clinical practice. These arrhythmias are the aim of the basic research and clinical studies for more than 100 years. Nevertheless, the mechanisms of AF/AFL initiations are still unknown and this may be the reason why prevention and treatment of these arrhythmias remain suboptimal.

Definitions

Atrial fibrillation is the most common supraventricular arrhythmia characterized by fast (350-700/min), electrically uncoordinated atrial activity which causes the loss of hemodynamic effective contraction of the atria. It is associated with irregular ventricular rate (fig. 1).

Atrial flutter is defined as regular, fast rhythm with an atrial rate of 240-350 per minute which arises in the reentry mechanism (fig. 2).

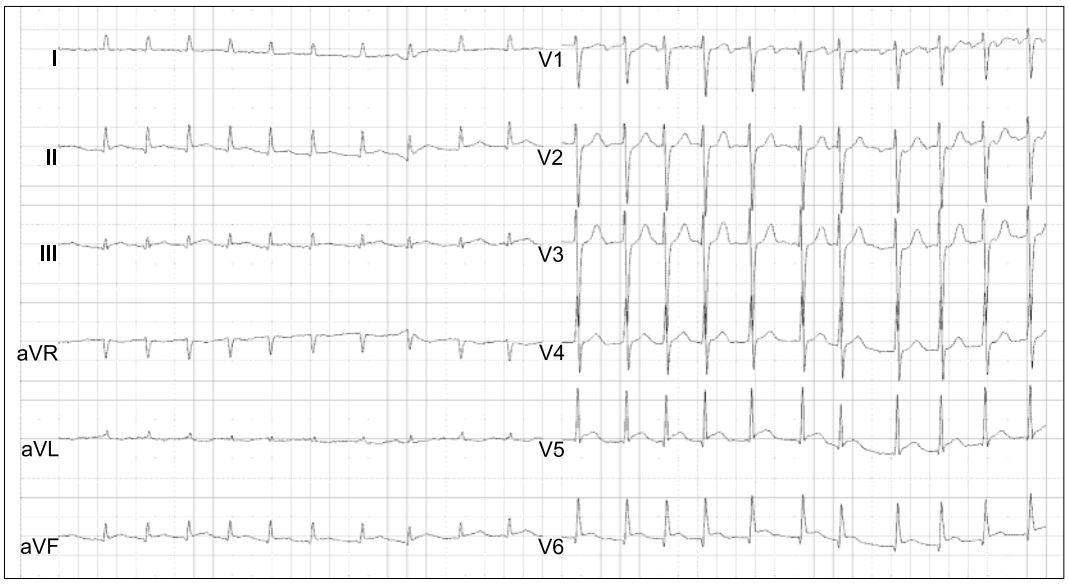

Fig. 1. Atrial fibrillation (AF).

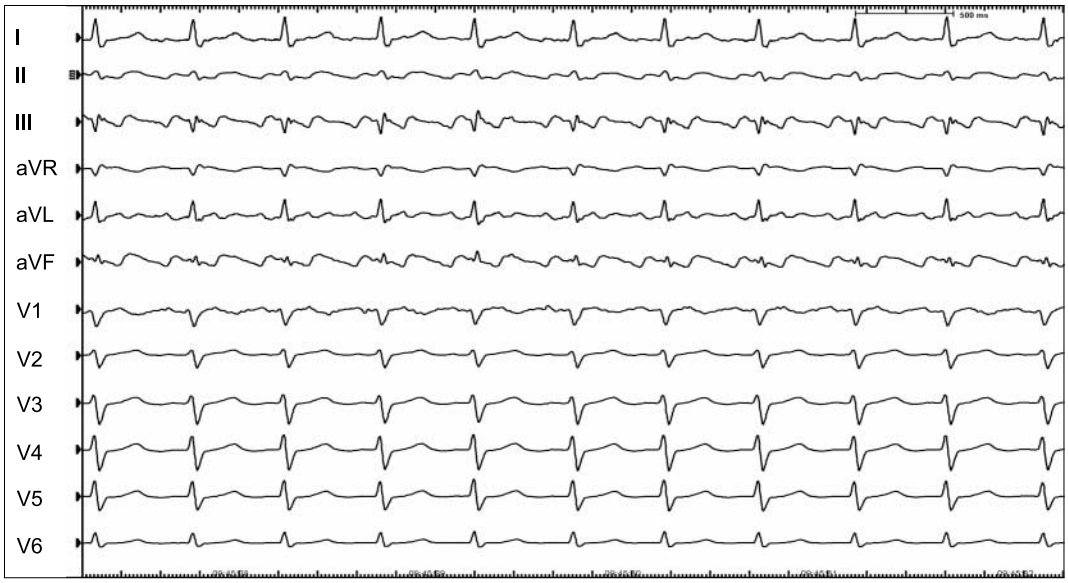

Fig. 2. Typical atrial flutter (AFL).

OCCURANCE

Atrial fibrillation poses one of the most common arrhythmia in clinical practice and often coexists with AFL (1-5). More than 6 million people in Europe suffer from AF. The incidence of this arrhythmia doubled in last five decades as a result of population ageing (6).

The incidence of AF/AFL increases with increasing age of patient – from < 0.5% at the age of 40-50 to 5-15% at the age of 80. It appears more common in women than the in men. The risk of AF in the people over 40 is about 25%. The incidence of AF is better known in caucasian race (6).

Predictive factors of AF/AFL are shown in table 1.

According the Polish Society of Cardiology (PTK) and European Society of Cardiology (ESC) (7), atrial fibrillation and atrial flutter can be divided in five types:

1. AF/AFL recognized for the first time – in the group of patients with the first episode of AF/AFL in life regardless of arrhythmia duration.

Table 1. Causes of AF/AFL.

Cardiac factors	Noncardiac factors
– Hypertension – Valvular heart disease (especially mitral valve disease) – Coronary heart disease – Cardiomiopathies – Congenital heart diseases – Myocarditis and pericarditis – History of cardiac surgery – Brady-tachy syndrome – Preexcitation – Systemic diseases affecting heart (ex. amyloidosis) – Primary and metastatic heart tumours	– Hyperthyreosis – Obstructive sleep apnoea – Acute infections – General anaesthesia – Pulmonary diseases – Pheochromocytoma – Alcohol, caffein, carbon monoxide, drugs (ex. β-mimetics) – Diabetes – Obesity

2. Paroxysmal AF/AFL – usually arrhythmia resolves by itself within 48 hour. It may last up to 7 days.

3. Persistent AF/AFL – usually arrhythmia lasts more than 7 days or requires pharmacological or electrical cardioversion (DCC).
4. Long-lasting persistent AF/AFL – arrhythmia lasting ≥ 1 year at the time of decision to return to sinus rhythm.
5. Permanent AF/AFL – arrhythmia accepted by patient and physician.

Atrial fibrillation and atrial flutter occurs as important clinical and population problem. It is responsible for increased risk of death, stroke, thromboembolic complications, development of heart failure, tachyarrhythmic cardiomyopathy, hospitalization and impairs quality of life. All patients from AF/AFL group need to be asses according to CHA2DS2-VASC score (8), in aspects of most common risk factor for stroke/TIA incidence in clinical practice, such as:

- Congestive heart failure,
- Hypertension,
- Age ≥ 75 years (2 pts),
- Diabetes,
- Stroke (2 pts)
- Vascular disease,
- Age 65-74 years,
- Sex category (female).

The risk for bleeding should be assessed in all patients from AF/AFL group and in the case of ≥ 3 points in HAS-BLED score (hypertension, abnormal kidney/liver function, stroke, bleeding or bleeding tendency in anamnesis, unstable INR, elderly, drugs/alcohol) the treatment should be ordered with special care, systematically repeated assessment of bleeding is necessary and potentially reversible risk factors should be corrected (8).

Among the group of patients with AF/AFL and ≥ 1 stroke risk factors, the anticoagulant treatment (NOAC/VKA) should be considered including risk/benefit ratio and patient's preferences (8).

It is estimated that every fifth stroke may be associated with cardiogenic embolism, where AF/AFL is responsible in 15% cases (9). Furthermore, silent arrhythmia (silent AF/AFL) may be responsible for clinically silent stroke.

Atrial fibrillation and atrial flutter may present in various clinical way and depend on presence or absence organic heart disease. The most common afflictions of supraventricular tachyarrhythmia are: fast heart beating named palpitation felt in rest and increasing in exercise, emotional stress, dyspnoea, chest pain, tiredness, dizziness and syncope. In clinical practice EHRA score is often used to assess the severity of symptoms associated with AF/AFl (10) (tab. 2).

Table 2. EHRA score.

EHRA I	"Asymptomatic"
EHRA II	"Mild symptoms". Daily activity not disturbed
EHRA III	"Severe symptoms". Daily activity disturbed
EHRA IV	Daily activity impossible due to symptoms

EHRA score takes into account only symptoms of the arrhythmia, resolved upon discontinuation of AF/AFL. Considering prevalence and clinical implications of AFL, this arrhythmia for many years been the focus of interest, both the mechanisms of arrhythmia and the related methods of treatment.

TISSUE MECHANISMS

Data from experimental and clinical studies revealed very complicated pathophysiological mechanism of AF pathogenesis. The most important are oxidative stress, calcium ions overloaded, enlarged/stretched atria, microRNA, inflammatory factors and miofibroblasts activation (11). All of them in one way or another, are probably responsible for remodeling phenomenon.

Atrial fibrillation and atrial flutter deteriorate function and gradually remodel the atria organ, tissues, cells and subcells (12). This is responsible for originating and maintaining of the arrhythmia (13, 14). Ausma et al. (14) observed first changes in cell structures after 7 days from the beginning of the arrhythmia. Those changes, called remodeling, increased with duration of AF. Remodeling shortens cardiomyocytes effective refractory time (electrical remodeling) what subsequently results in easier and more stable induction of arrhythmia. Electrical remodeling in sustained AF impairs atrial contractility, which is an important clinical fact when returning to sinus rhythm. The disease lasting over weeks/months leads to structural remodeling (15). In structural remodeling, the presence of fibrous connective tissue may explain the interatrial conduction disorders and a tendency to AF (16). Structural remodeling induced by AF and caused by organic cardiac disease is responsible for development of arrhythmia's substrate.

Paroxysmal forms of the arrhythmia are related with triggers, located especially in pulmonary veins (PVs). In case of transition of arrhythmia to persistent or permanent forms, functional and later also structural substrate mechanisms dominate, what enables to initiate reentry (fig. 3). Data showed that initiation of AF due to premature impulse from pulmonary vein, whether by fast atrial stimulation or in another mechanism, revealed oxidative stress as a first consequence of fast atrial electrical activity. Reactive Oxygen Species (ROS) are responsible for rapid (hours or days) changes in ionic currents, shortening atrial action potential and refractory period, which enables initiation and stabilization of rotors. It leads to calcium Ca^{2+} ions overload of cardiomyocytes and favors triggered activity and apoptosis (18).

During persistent AF, high electrical activity rate caused by rotor (-es) activity leads to resistance of rianodine cardiac receptors (RyR2) (19) located in the sarcoplasmatic reticulum as well as to downregulation of the proteins responsible for cellular Ca^{2+} (20-22), circulation that prevent triggered activity.

Nevertheless, overloading with Ca^{2+} ions combined with atrial enlargement, mitochondrial ROS and initiation of inflammatory process enable fibrosis (23) and gradual change in gens expression.

MicroRNA is a group of naturally occurring, noncoding RNA molecules that are partially complementary to

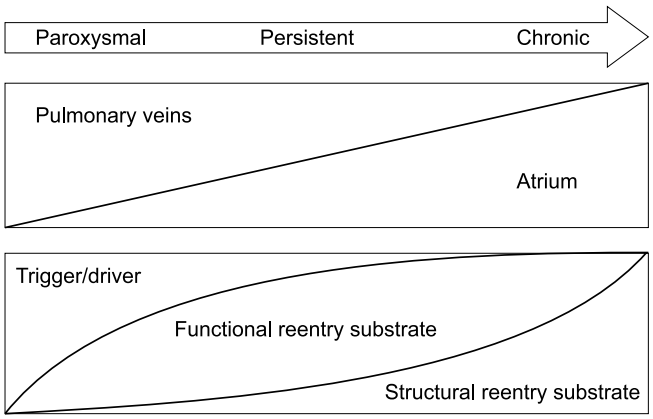

Fig. 3. Clinical forms of arrhythmias and their mechanisms (17).

one or more transmitting RNA (mRNA) (24). The main role of microRNAs is to control the transcription of proteins by specific degradation of mRNA. Available data indicate the important role of microRNAs in cardiovascular disease, including AF (25). Myofibroblasts producing and releasing a certain type of microRNA, called microRNA-21 can result in hypertrophy and fibrosis of myocardium (26). Increased expression of microRNA-21 has also been shown in patients with AF (27).

Recent studies based on an animal model of permanent AF, showed that amendments may be consequences of: myocyte hypertrophy, intercellular fibrosis, as well as changes in the ion channels (electrical remodeling). All these processes take place relatively slowly, but at some point reach a critical level when the AF lasts long enough, with a median of approximately 2 months (20).

Time, the progress of remodeling, permanent changes associated with the expression of ion channels, structural changes including atria, lead to the maintenance of the electrical activation of high frequency within the atria and, as a result, the mechanism of the "vicious circle" that further stabilize the rotors, fibrosis and maintenance of AF.

CONCLUSIONS

The increasing incidence of AF/AFL augments the scientific interest on etiology and pathogenesis of AF/AFL. In most cases AF/AFL begins as paroxysmal arrhythmia, whereas in many cases it then develops to persistent or permanent forms and reflects progressive electrophysiological and structural remodeling of the atria. It leads to stabilization and preserving of the sources of arrhythmia. Nevertheless, it is still unknown when and how the mentioned mechanisms, which participate in remodeling process, lead arrhythmia to persistent forms. Further investigations over mechanisms are necessary to understand complete etiology and pathogenesis of AF/AFL and improve preventive and treatment of the arrhythmia.

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received/otrzymano: 08.06.2015
accepted/zaakceptowano: 09.07.2015