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Recent Biotechnological Approach to Genetically Determined Atrial Fibrillation

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***Abstract*—Background. The most prevalent persistent arrhythmia in cardiology is atrial fibrillation. Former atrial fibrillation which appears without any underlying reason was called „lone atrial fibrillation". Due to new biotechnological methods in electrophysiology, like mapping, unusual conducting mechanisms were stabilized. Due to new biotechnological methods of DNA analysis recently the reason is detected. This is a genetically determined atrial fibrillation. The aim of this study is to analyse what are the most common mutations which lead to atrial fibrillation. Material and methods. This is a systematic review study. The sources of information which were analysed are mostly from google scholar and web of science. From 2000 sources, several sources were filtered out by the keywords and remained 14 sources on which is based this review study. Results. More than 70 genes are recently detected which lead to atrial fibrillations. Majority of them are mutations of the genes which encode the transport proteins of the heart's conductive system. The most common mutations that lead to genetically determined atrial fibrillation occure in KCNQ1, KCNA5 and 6q14–16. Conclusions. Before starting treatment of lone atrial fibrillation, a genetical test should be done in order to stabilize the type of the underlying mutation. This is a tactical step in taking the decision on treatment strategy by antiarrhytmic drugs or ablation. So ablatogenoics is the best solution for patients with genetically determined atrial fibrillation.**

Keywords: Atrial Fibrillation, genetic predisposition, gene mutation, ablatogenomics, biotechnological tools.

I. INTRODUCTION

The most prevalent persistent arrhythmia in cardiology is atrial fibrillation affects approximately six million individuals within European Union [1]. According to the "Worldwide Epidemiology of Atrial Fibrillation: Global Burden of Disease" research from 2013, 33.5 million individuals worldwide, or around 0.5 percent of the world's population have atrial fibrillation. 25% of persons over the age of 40 will have the illness at some point in their lives, and it is linked to significant morbidity and a roughly doubled death rate [2]. Although the impact of structural heart determinants on the arrhythmogenesis of atrial fibrillation is well defined [3], it's important to know the circumstances that lead to atrial fibrillation in individuals who don't have any obvious structural heart abnormalities, this is the so-called was called „lone atrial fibrillation [4]. Wolff reported a family of three brothers with atrial fibrillation in one of the first studies of an inherited type of atrial fibrillation published in 1936. The first gene mutation related with familial atrial fibrillation was identified in the KCNQ1 gene, which codes for the Kv7.1 potassium channel that mediates the slow rectifying potassium current [5]. Other ion channel genes involved in atrial fibrillation include the sodium channel encoding gene SCN5A. In a Japanese family with autosomal dominant familial atrial fibrillation, for example, an unique gain-of-function mutation in SCN5A (M1875T) was found [5]. 5% of the unselected atrial fibrillation population has SCN5A mutations, with a greater incidence in younger cohorts. Also related with atrial fibrillation are single-nucleotide polymorphisms encoding sodium channels (SCN family) [5, 6]. Intriguingly, a loss-of-function mutation in the potassium voltage-gated channel, shaker-related subfamily member 5 (KCNA5) affected tyrosine kinase regulation, indicating that malfunctioning ion channels are not the only cause of cardiac electrophysiological disturbances [5]. Later investigations found additional genetic loci linked to atrial fibrillation at 6q14–16, 5p13, 10p11–q21,

20q12–13, and 5p15 [6]. The first gain of function mutation (KCNQ1) in the potassium voltage-gated channel in the afflicted Chinese family was described by Chen et al. in 2003. The candidate gene study, however, was expensive, time-consuming, and limited to a few selected scanning genes. Additionally, since potassium channel genes contain more than 30 distinct variations, the causation impact hypothesis of these variants remained unclear [6]. It is important to determine what type of gene mutation causes the atrial fibrillation. The reason is that individuals with genetically determined atrial fibrillation do not react in an expected way to antiarrhytmic drugs, even vice versa, by proarhhythmic effect [7]. This is dangerously as the consequences are hard to predict if no information about the type of mutation. The aim of this study is to analyse what are the most common mutations which lead to atrial fibrillation.

II. ATRIAL FIBRILLATION CAUSED BY GENE MUTATION

A. Potassium Channel Mutations

Several mutations in potassium channel subunits have been linked to uncommon types of atrial fibrillation [7]. Several mutations in potassium channel subunits have been linked to uncommon types of atrial fibrillation [8]. In addition to having a role in the various stages of repolarization, the various potassium channel subtypes expressed on cardiac cells are crucial for maintaining resting membrane potential [9]. Potassium channels are made of subunits that constitute the pore as well as several additional partner proteins, including accessory subunits. Two to six transmembrane domains arranged as dimers and tetramers comprise the entire channel's subunits [8]. IKs, the delayedrectifier potassium current, is one of the earliest ion channel mutations that have been investigated [5]. Gainoffunction mutations in both subunits boost potassium repolarizing currents mechanistically. This shortens the action potential duration and effective refractory period in cardiomyocytes, producing a substrate for profibrillation in the atria [9].

B. Mutations Involving the Rapidly Repolarizing Potassium Current

The potassium voltagegated channel subfamily H member 2 (KCNH2) gene encoding the subunit of the voltagegated potassium channel Kv11.1, which causes the quickly repolarizing potassium current [9, 10]. KCNH2 gene mutations are associated with a greater risk of atrial fibrillation. In a family with short QT syndrome and atrial fibrillation, a mutation in the KCNH2 gene causing in a gain of function of the rapidly repolarizing potassium channel was also identified [7]. This gainoffunction mutation causes a reduction in APD length [9]. Atrial fibrillation has also been related to a mutation in the KCNH2 gene that results in a lack of function [11].

III. BASIS OF THE HEART'S ELECTRICAL CONDUCTION SYSTEM

At the point where the superior vena cava enters the right atrium, pacemaker cells of the SA node depolarize spontaneously to provide electrical impulses that begin regular cardiac rhythm [3]. Then, the signals are sent to the AV node in the posteroinferior area of the interatrial septum. The AV node retards the transmission of the electrical signal to the ventricles, allowing for the optimum fill of the ventricles. The signal then propagates via the left and right bundles of His, followed by the left and right ventricular Purkinje fibers [12]. These signals are subsequently carried through the membranes of cardiac myocytes. The movement of sodium, calcium, and potassium ions significantly affects the cardiac action potential[3, 8]. Every phase of the action potential is caused by a significant ionic current. Through adherens junctions and desmosomes, intercalated disks among myocytes provide celltocell adhesion and bind the cytoskeletal structures to the cell membrane [13]. M oreover, they coordinate the movement of ions and tiny molecules across cells through other proteins. 5 Ion transfer is crucial to the propagation of the action potential [13].

IV. TREATMENT STRATEGY

A. Rate Control

A In general, a resting heart rate of up to 80 beats per minute and an exercise heart rate of up to 115 beats per minute are appropriate targets for ventricular rate management in atrial fibrillation [3]. Mobile telemetry is advised for objectively assessing atrial fibrillation - heart failure patients [2, 3]. Traditionally, beta-blockers have been used to moderate heart rate, especially in patients with heart failure, unless they are rapidly decompensated, and they are effective either alone or in conjunction with other medications in the majority of patients [2]. Particularly with exercise, rate control may be a tough objective to attain in actual clinical practice. No pharmacological class is universally successful, and combination therapy or other treatments are necessary to ease symptoms [4]. Current recommendations prescribe beta-blockers strongly for people with HFrEF (class I, level of evidence A) [10]. Rate control is the use of negatively chronotropic medicines or electrophysiological/surgical techniques to lower the often fast ventricular rate in atrial fibrillation patients [11].

B. Rhythm Control

A strategy of rate control alone may not be enough to treat atrial fibrillation-mediated cardiomyopathy or chronic symptoms [11]. Rhythm regulation, whether done pharmacologically, with electrical cardioversion, or catheter ablation, has been demonstrated to improve LV dysfunction and have a positive influence on survival and quality of life [12]. The goal of the rate control technique is to solely lower ventricular rates brought on by atrial fibrillation [11]. The CAFÉ-II trial found evidence that rhythm control is associated with better quality of life (p=0.020) and LV function (p=0.014) in heart failure patients, despite the restricted number of participants [12]. The biggest effect was noticed in patients who maintained sinus rhythm for one year. Compared to amiodarone alone, adjunctive treatment with cardioversion and amiodarone restored and maintained sinus rhythm at 1 year with a higher success rate (80% v/s 66%) [12, 13].

V. BIOTECHNOLOGICAL ADVANCES IN ELECTROPHYSIOLOGY FOR IDENTIFYING THE CONDUCTIVE ABNORMALITY IN ATRIAL FIBRILLATION

In order to comprehend this complicated arrhythmia, the electrophysiology of atrial fibrillation has remained a profound enigma [6]. Despite substantial investigation, the pathophysiological causes of atrial fibrillation are complicated and frequently remain unexplained [2, 10]. Therefore, the application of fundamental scientific information to clinical practice is difficult [2]. After more than two decades, pulmonary vein isolation remains the primary ablation technique for preserving sinus rhythm [12, 13]. There is little question, however, that in many instances, particularly in chronic and long-standing persistent atrial fibrillation, ablation by pulmonary vein isolation is insufficient, and the final restoration of SR requires further intervention in the remainder of the atrial myocardium [4, 12]. Substrate mapping is a contemporary problem because it might uncover focused sources of rotational activity that may be responsible for the maintenance of atrial fibrillation. It is uncertain if these regions are the true source of the atrial fibrillation maintenance. If this is the case, then focused ablation may be the best option [10]; alternatively, more invasive procedures, such as atrial compartmentalization, may be more helpful. Catheter ablation for atrial fibrillation is an invasive technique that is successful at restoring normal rhythm, but it fails in up to 40% of patients receiving their first surgery and bears the risk of major side outcomes [3, 10]. Recent research indicates that a common genetic mutation on chromosome 4q25 may be a robust predictor of procedural success, underlining the promise of a "ablatogenomic" method [8, 13].

CONCLUSIONS

1. New biotechnological methods of DNA analysis made possible to detect that gene mutations are the reason of „lone atrial fibrillation“.
2. The most common mutations that lead to genetically determined atrial fibrillation occure in KCNQ1, KCNA5 and 6q14–16.
3. Before starting treatment of lone atrial fibrillation, a genetical test should be done in order to stabilize the type of the underlying mutation.
4. Gene analysis to determine the type of mutation is a tactical step in taking the decision on treatment strategy by antiarrhytmic drugs or ablation.
5. Ablatogenomics is the best solution for patients with genetically determined atrial fibrillation.

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