A Short Review of Management of Cardiac Arrhythmia

Rahul Khanna*1, Iftekhar Kalsekar*, Abhishek Chitnis1

1Department of Geriatrics and Cardiology

*Corresponding Author : Rahul Khanna, Department of Geriatrics and Cardiology E-mail: rkhan14@its.jn.com

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Abstract

During the past few years, the development of effective, empirical technologies for treatment of cardiac arrhythmias has exceeded the pace at which detailed knowledge of the underlying biology has accumulated. As a result, although some clinical arrhythmias can be cured with techniques such as catheter ablation, drug treatment and prediction of the risk of sudden death remain fairly primitive. The identification of key candidate genes for monogenic arrhythmia syndromes shows that to bring basic biology to the clinic is a powerful approach. Increasingly sophisticated experimental models and methods of measurement, including stem cell–based models of human cardiac arrhythmias, are being deployed to study how perturbations in several biologic pathways can result in an arrhythmia-prone heart. The biology of arrhythmia is largely quantifiable, which allows for systematic analysis that could transform treatment strategies that are often still empirical into management based on molecular evidence.

Introduction

Effective treatment is now available for many arrhythmias. Devices and sophisticated catheters, together with computerised-mapping systems that allow for ablation therapy, have brought some remarkable advances. Such technologies have transformed clinical electrophysiology into one of the most rapidly expanding cardiology subspecialties. Pacemakers are the accepted standard of care for those with bradycardia, and if facilities are available, patients with Wolff-Parkinson-White syndrome or similar arrhythmias should be referred for ablation. Many complex atrial and ventricular arrhythmias are also amenable to potential cure with these approaches. These successes are all causes for celebration.

However, knowledge of the underlying biology has not kept up with technical developments, and major questions about clinical management remain. First, although we know some of the general factors that predispose to arrhythmias, the precision of our analysis is not always sufficient to justify prophylaxis or intervention. Second, if we want to suppress arrhythmia not amenable to ablation, we have few options. The range of available drugs has scarcely expanded in the past 30 years, and available drug treatments have proarrhythmic risk, other toxic effects, low tolerability, and variable (although never better than modest) efficacy. The generally poor outcomes with contemporary drug therapy are understandable, since most agents were developed in the absence of molecular targets and without precise understanding of the mechanisms of proarrhythmic and antianthyrhythmic drug actions. Finally, we are incapable of accurately identifying those at risk of sudden cardiac death (which is almost always caused by arrhythmia), which leaves the effective—but crude and expensive—option of implantable cardioverter defibrillators as the only viable choice for many. Thus, although some parts of contemporary arrhythmia care can be successful and provide seemingly definitive solutions, others will be seen in retrospect as fairly primitive.

Systematic approaches to cardiac arrhythmias

The definition of systems biology remains contentious and is a subject of continued discussion. For practical purposes, we define systems biology as an analytical framework that is characterised by integrated descriptions of several biological processes that are based on systematic measurements. Applied to medicine, the approach necessitates as a starting point large, high-quality datasets that describe the phenotypes and natural history of a disease, in this case cardiac arrhythmia.

If necessary, revised diagnostic categories might be used to describe specific entities more precisely. These data are combined with results of genetic, genomic, or other molecular analyses and complemented with work from experimental systems, ideally of human origin, which can model functional consequences. The properties of such models can then be examined in response to either potentially deleterious changes or interventions (such as drugs) intended to rescue the disease phenotype.

Population-based risk of atrial fibrillation and sudden cardiac death

Atrial fibrillation is the most common sustained arrhythmia. It is age-related, with a life-time risk estimated at 25% for a 40-year-old person. The most serious chronic disease sequelae of atrial fibrillation include stroke, heart failure, and dementia—all of which have devastating effects on an individual’s health and high costs for families and society. Two broad categories of atrial fibrillation are seen in clinical settings. One is a small group of usually comparatively young patients, who often have a family history of the disease and might also have a history of high-intensity exercise. However, most patients belong to the second group of usually older individuals, the numbers of whom are growing.

Cellular Origin of Early Afterdepolarizations

EADs develop more commonly in midmyocardial M cells and Purkinje fibers than in epicardial or endocardial cells when exposed to action potential duration (APD)-prolonging agents. This is because of the presence of a weaker Ik and stronger late Is in M cells, Block of Ik with chromanol 293B permits the induction of EADs in canine epicardial and endocardial tissues in response to Ik blockers such as E-4031 or sotalol. The predisposition of cardiac cells to the development of EADs depends principally on the reduced availability of Ik and Ik, as occurs in many forms of cardiomyopathy. Under these conditions, EADs can appear in any part of the ventricular myocardium.

Role of Delayed Afterdepolarization-Induced Triggered Activity in the Development of Cardiac Arrhythmias

An example of DAD-induced arrhythmia is the catecholaminergic polymorphic ventricular tachycardia (CPVT), which may be caused by the mutation of either the type 2 ryanodine receptor (RyR2) or the calsequestrin (CSQ2). The principal mechanism underlying these arrhythmias is the “leaky” ryanodine receptor, which is aggravated during catecholamine stimulation.

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A typical clinical phenotype of CPVT is bidirectional ventricular tachycardia, which is also seen in digitalis toxicity. Wehrens and colleagues demonstrated that heterozygous mutation of FKBP12.6 leads to leaky RyR2 and exercise-induced VT and VF, simulating the human CPVT phenotype. RyR2 stabilization with a derivative of 1,4-benzothiazepine (JTV519) increased the affinity of calstabin2 for RyR2, which stabilized the closed state of RyR2 and prevented the Ca leak that triggers arrhythmias.

**Ttractable model systems**

Computer models of heart function that incorporate equations to describe activity of individual ion channels or transporters are well established. However, collection of high-quality data from the full range of relevant animal species to populate the models has been difficult. Ideally, these data should include descriptions of the function, expression, interactions, and metabolic status of individual proteins. Because human tissue is difficult to obtain, heterologous expression of ion channels in non-human cells with complementary studies in wild type and genetically modified animals have had to suffice for detailed functional studies.

**Developing new treatments**

An important aim of the development of disease models is to allow responses to therapeutic interventions to be assessed. New models, combined with other features of a systems approach, might well identify molecules targeting of which could be antiarrhythmic. These insights might come from family or population genetic approaches, or from laboratory studies of proarrhythmia. These insights could then be assessed in wild-type or genetically modified animals and genetically modified animals have had to suffice for detailed functional studies.

**Conclusions**

Systematic approaches to human disease are at an early stage, but they offer the possibility of refined diagnosis, risk prediction, and targeted treatment decisions (figure 1). We believe that cardiac arrhythmias are especially amenable to a systems biology approach, partly because of the range of measurable determinants. Next-generation sequencing, exploitation of stem cell-based models, and new uses of omics technologies are starting to provide tangible evidence of what can be achieved. The use of these experimental technologies in combination with holistic, network-based approaches can be used to find rational solutions to many of the unresolved questions in arrhythmia management.

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