Journal of Molecular and Cellular Cardiology 82 (2015) 136–152

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review Article

Perspective: A dynamics-based classification of ventricular arrhythmias

James N. Weiss [a,b,*], Alan Garfinkel [a,c], Hrayr S. Karagueuzian [a], Thao P. Nguyen [a], Riccardo Olcese [b,d], Peng-Sheng Chen [e], Zhilin Qu [a]

[a] UCLA Cardiovascular Research Laboratory, Department of Medicine (Cardiology), UCLA and the David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[b] Department of Physiology, UCLA and the David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[c] Department of Integrative Biology and Physiology, UCLA and the David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[d] Department of Anesthesiology, UCLA and the David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[e] Krannert Institute of Cardiology and Department of Medicine (Cardiology), Indiana University School of Medicine, Indianapolis, IN, United States

ARTICLE INFO

Article history:
Received 9 December 2014
Received in revised form 5 February 2015
Accepted 20 February 2015
Available online 11 March 2015

Keywords:
Nonlinear dynamics
Fibrillation
Reentry
Repolarization reserve
Ca signaling
Sudden cardiac death

ABSTRACT

Despite key advances in the clinical management of life-threatening ventricular arrhythmias, culminating with the development of implantable cardioverter-defibrillators and catheter ablation techniques, pharmacologic/biologic therapeutics have lagged behind. The fundamental issue is that biological targets are molecular factors. Diseases, however, represent emergent properties at the scale of the organism that result from dynamic interactions between multiple constantly changing molecular factors. For a pharmacologic/biologic therapy to be effective, it must target the dynamic processes that underlie the disease. Here we propose a classification of ventricular arrhythmias that is based on our current understanding of the dynamics occurring at the subcellular, cellular, tissue and organism scales, which cause arrhythmias by simultaneously generating arrhythmia triggers and exacerbating tissue vulnerability. The goal is to create a framework that systematically links these key dynamic factors together with fixed factors (structural and electrophysiological heterogeneity) synergistically promoting electrical dispersion and increased arrhythmia risk to molecular factors that can serve as biological targets. We classify ventricular arrhythmias into three primary dynamic categories related generally to unstable Ca cycling, reduced repolarization, and excess repolarization, respectively. The clinical syndromes, arrhythmia mechanisms, dynamic factors and what is known about their molecular counterparts are discussed. Based on this framework, we propose a computational–experimental strategy for exploring the links between molecular factors, fixed factors and dynamic factors that underlie life-threatening ventricular arrhythmias. The ultimate objective is to facilitate drug development by creating an *in silico* platform to evaluate and predict comprehensively how molecular interventions affect not only a single targeted arrhythmia, but all primary arrhythmia dynamics categories as well as normal cardiac excitation–contraction coupling.

Contents

Abbreviations: AP, Action potential; APD, AP duration; BS, Brugada syndrome; CaMKII, Ca-calmodulin kinase II; CPVT, Catecholaminergic polymorphic ventricular tachycardia; CV, Conduction velocity; DAD, Delayed afterdepolarization; EAD, Early afterdepolarization; ERS, Early repolarization syndrome; ICD, Implantable cardioverter-defibrillator; $I_{Ca,L}$, L-type Ca current; I_{Kr}, Rapid component of the delayed rectifier K current; I_{Ks}, Slow component of the delayed rectifier K current; I_{Na}, Na current; I_{to}, Transient outward K current; LQT, long QT; NCX, Na–Ca exchanger; PVC, Premature ventricular complex; RyR, Ryanodine receptor; SERCA, Sarco-endoplasmic reticulum Ca ATPase; SQT, Short QT; SR, Sarcoplasmic reticulum; VF, Ventricular fibrillation; VT, Ventricular tachycardia.

* Corresponding author at: Division of Cardiology, 3645 MRL Bldg, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States. Tel.: +1 310 825-9029; fax: +1 310 206 5777.
E-mail address: jweiss@mednet.ucla.edu (J.N. Weiss).

http://dx.doi.org/10.1016/j.yjmcc.2015.02.017
0022-2828/

1. Introduction

With the advent in the 1940s and 1950s of intracellular microelectrode recordings and the development in subsequent decades of sophisticated arrhythmia mapping and imaging techniques, followed by the blossoming of molecular ion channel biophysics and computational biology, a wealth of information about arrhythmia mechanisms at the molecular, cellular, organ and organism scales has come to light [1–6]. Based on this research, major advances in arrhythmia treatment have occurred over the past century, culminating with the development of surgical and catheter ablation techniques and implantable cardioverter-defibrillators (ICDs). Pharmacologic/biologic approaches to treat arrhythmias, however, have lagged behind. Well-designed clinical trials, such as CAST [7] and SWORD [8], revealed that promising agents that were effective at suppressing one arrhythmia mechanism proved to be proarrhythmic by exacerbating other mechanisms. As a result, the enthusiasm of the pharmaceutical industry for antiarrhythmic drug development has been severely curtailed. Yet the need is clearly there. Ablation is curative for some arrhythmias, but others do not have discrete anatomical structures to target. Device therapy is also not ideal, since ICDs terminate arrhythmias effectively, but do not prevent them. Moreover, 80% of patients who will die suddenly each year do not meet clinical indications (i.e. low ejection fraction or prior documented arrhythmia history) for implanting an ICD [9]. Of the ones who do, only one of five ICDs implanted will actually deliver a life-saving shock due to the difficulty in predicting which patients are at the greatest risk [10].

Why has the development of effective antiarrhythmic drugs been so frustrating? The generic challenge in controlling or curing any disease pharmacologically is that drugs target molecules, but diseases occur at the organism scale, and the relationship between the behavior of a molecule and the behavior of an organism is hardly straightforward. In the case of arrhythmias, electrophysiological properties that determine the likelihood of an arrhythmia at the tissue level are not directly controlled in a straightforward way by single molecules. Rather, very complex nonlinear interactions between many molecules first integrate to produce the electrophysiological properties at the level of the cell, including the action potential (AP), Ca cycling features, automaticity, early (EAD) and delayed (DAD) afterdepolarizations, excitability and refractoriness, etc. These cellular electrophysiological factors next integrate, again in complex nonlinear ways, to generate the tissue electrophysiological properties, including excitability characteristics, conduction properties, dispersion of refractoriness, electrical alternans and a variety of other factors impacting the initiation and maintenance of cardiac arrhythmias. Meanwhile, other organ systems in the body are constantly dynamically modulating these factors at the molecular, cellular and organ scales through autonomic tone, electrolyte balance, various endocrine functions, etc. Given the complexity of the system, predicting how modifying a single target molecule will impact the behavior of the overall system is a daunting task. Despite this complexity, however, successful precedents exist. For example, beta blockers targeting the beta adrenergic receptor, and drugs inhibiting angiotensin-converting enzyme (ACE) and antagonizing the hormone aldosterone have been proven to reduce the incidence of sudden cardiac death in large cohorts of patients with heart failure and ischemic heart disease [11]. Unfortunately, we have been much less successful with drugs targeting the ion channels that directly influence cardiac electrophysiological properties, possibly because available pre-clinical experimental and clinical arrhythmia induction paradigms incompletely recapitulate clinical arrhythmias.

Can this impasse be broken? In our view, to make substantive progress will require a comprehensive analysis linking the function of molecules, the material entities such as ion channels or receptors that can be targeted by drugs or biologics, to electrophysiological factors that determine arrhythmia risk at the organism scale. This is an inherently multiscale problem which requires linking molecular factors first to electrophysiological and structural factors at the subcellular scale (e.g. Ca cycling properties), then to factors at the cellular scale (e.g. action potential properties), next to factors at the tissue scale (e.g. conduction properties), and finally factors to the organism scale (e.g. autonomic and metabolic properties) [6]. An advantage of the arrhythmia field, compared to many other disease areas, is that we already have a fairly detailed understanding of the electrophysiological and structural factors at the subcellular, cellular, organ and organism levels that promote arrhythmias. What is lacking is an integrated framework for evaluating and predicting how the behaviors of proteins at the molecular scale are linked to the relevant electrophysiological and structural factors promoting arrhythmias at the subcellular/cellular/organ/organism scales. Too often antiarrhythmic drug development strategies have focused on one arrhythmia mechanism without considering, in any systematic way, how the drug may impact other arrhythmia mechanisms. For example, the CAST study [7] evaluating Na channel blockers was based on the premise that suppressing premature ventricular complexes (PVCs), the triggers that initiate reentry, should decrease the incidence of reentrant ventricular tachycardia (VT) and fibrillation (VF). This was a very reasonable hypothesis, but failed to take into account the effects of Na channel blockers on the tissue substrate. We know now that Na channel blockers increase the vulnerability of the tissue to initiation of reentry. Thus, if the PVC