Editorial

Blunderbuss to Mickey Mouse
The Evolution of Antiarrhythmic Targets

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In an era that finds us continually bombarded with numbers and images about threats, both real and imagined, a threat as old as the Bible that continues its dangerous course is that of cardiac arrhythmia.

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- “... [My] heart trembleth and is moved out of its place.” said Elihu in the Book of Job1; if not a run of ventricular tachycardia, perhaps a paroxysm of atrial fibrillation.

- “Palpitations rebelles” respond favorably to a suspension of cinchona and rhubarb, noted Senac in 1749;2 thereby demonstrating the effect of a quinidine-like molecule on what was presumably atrial fibrillation.

- Quinidine terminates episodes of palpitations, said a patient to Wenckebach in 1914, and in 1918, Frey observed the superiority of quinidine to quinine as an antiarrhythmic agent. In testing quinidine, he used a drug developed by Pasteur in 1853 as an antimalarial alternative to quinine and cinchona.2

The year of Wenckebach’s observation,1 1914, was the same year in which George Ralph Mines3 published his initial experiments on reentry, observations on “circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation” that were seminal to the field. That year was little more than a decade after Einthoven’s description of the ECG,4,5 which rapidly became and has remained the primary tool facilitating both our understanding and our diagnosis of arrhythmias during these 100 years since its invention.

The decades after the first therapeutic application of quinidine saw the testing and addition to arrhythmia therapy of drugs such as procaine, procainamide, ajmaline, and diphenylhydantoin.2 By the end of the 1960s, with propanolol and lidocaine available, there seemed to be great promise in the evolution of meaningful drug treatment. This was not only the product of work in drug development, but also of research using microelectrodes to record from cells and studies using animal models that informed us about the mechanisms of drug action (permitting their classification) and the mechanisms responsible for arrhythmias. Lidocaine and β-blockers had come onto the scene, and disopyramide, flecainide, and the calcium channel blockers were soon to follow; it seemed like the bad old days of quinidine and procaineamide were to give way to a new beginning.

The dousing of our optimism came quickly. Use of the then-new Holter monitoring technique demonstrated that we knew far less about the expression of arrhythmias than we had thought. Replacement of the 2-minute rhythm strip by 4-hour, then 6-hour, and finally 24 hour or longer periods of monitoring showed us that arrhythmias could be quantified and considered in terms of their reproducibility and that drug effects could be measured in far more convincing fashion than we had previously thought.6,7 We also learned that much of what we had interpreted as antiarrhythmic efficacy in fact reflected placebo effect and/or the inherent variation in arrhythmia expression over time.

Next came the Cardiac Arrhythmia Suppression Trial (CAST),8 which had 2 outcomes. First, it showed us the dark side of administering antiarrhythmic drugs (in this case flecainide, encaainide, and moricizine) to patient populations not truly in need of them. Second, it reinforced a mindset that strove to develop drugs mimicking the repolarization-prolonging effects of amiodarone, which was reported as an antiarrhythmic agent in 1969.9 This intent to prolong repolarization, (the class III effect of Singh and Vaughan Williams10,11 led to the clinical testing of the uniquely 1K Na-blocking derivative of sotalol, d-sotalol. The resultant Survival With Oral d-Sotalol (SWORD) trial,12 in which mortality in the d-sotalol-treatment group was excessive, not only mirrored the CAST experience for a different patient population but further dampened the enthusiasm for new antiarrhythmic drug development. Nonetheless, some apparently useful drugs (eg, dofetilide,13 ibutilide,14 and azimilide15) have evolved from the effort to prolong repolarization and, in some instances, have been approved for patient care.

In part, the limited development of new drugs was the result of industry’s post-CAST and SWORD lack of enthusiasm coupled with a lack of imagination in industrial and academic basic science. So constrained was our vision regarding targets for antiarrhythmic development that the old adage “if the only tool you have is a hammer, then everything looks like a nail” could have been used to characterize the field. There was recognition of the need for new targets, and though investigators called for them and wrote of them,16,17 they seemed not to come.

Hence, there evolved a major disconnect between need for novel and safe antiarrhythmic drug therapy and satisfaction of this need. Recently, this need has been emphasized by the Communicable Disease Center, which tells us of 420 000 sudden deaths per year in the United States alone that are...
presumably the result of arrhythmia. It is seen in the statistics showing that atrial fibrillation afflicts 5% or more of the population over 65 years of age. It is highlighted by the fact that myocardial infarction and its associated arrhythmias, remain a scourge, while knowledge of the multiple incarnations of cardiomyopathy increasingly assails us. What many of these arrhythmic settings have in common is an element of myocardial hypertrophy. Such hypertrophy may be global, as in systemic hypertension; it may be regional, as in sepal hypertrophy; or it may be subtler, as in the localized hypertrophy that characterizes peri-infarct zones. Arrhythmias occur in all of these conditions. To deal with them, we have on hand a panoply of drugs that is as applicable to our current knowledge of arrhythmias as the blunderbuss is to our current knowledge of firearms.

Think of the above scenario in light of what we are beginning to understand. Arrhythmias are not the entities we once considered them to be, not a happening we can understand purely in light of animal electricity. They derive from a complex interaction of molecules that either directly impact electrical activity (by synthesizing the channels and pumps that transfer ions and charge) or indirectly impact electrical activity by influencing and modulating the activity of these molecules. We now understand that atrial fibrillation is not a single arrhythmia, despite the fact that it often has a typical pattern electrocardiographically. The same can be said for ventricular tachycardia. This statement is readily understood if we recognize that torsades de points resulting from congenital long-QT syndrome may derive from any one of a number of lesions in different channel proteins (eg, SCN5A, HERG, KVLQT1, etc), each of which is, in effect, a different disease. This syndrome has also taught us that it is not always enough to have a molecular lesion (ie, an anomaly of the substrate), but that a trigger may be necessary to bring about clinical expression. This is seen in the effect of sympathetic stimulation via β-adrenergic pathways to tip the balance in favor of torsades de points in KVLQT1-associated long-QT syndrome.

As we hunt for targets, most of these likely as old as Job, albeit new to us, and as we explore the diversity within the human heart, we need to pull together the threads of disease, hypertrophy, and arrhythmia and further conceptualize them in light of substrate and trigger. In engaging in such thinking, one can appreciate the value of the recent work on calmodulin of Wu et al. It is attractive for several reasons, combining, as it does, imagination, effort, and success.

In this issue of Circulation, Wu et al report studies of a mouse that overexpresses calmodulin kinase IV (CaMKIV) and develops ventricular hypertrophy. It also has increased endogenous CaMKII activity. Important to our understanding of this model’s value is the fact that CaMKII is associated with cardiomyopathy of diverse causes in human subjects, as well as in animal models. Also important is the central role of CaMKII as a “multifunctional kinase” that induces change at the level of nucleus, cytoskeleton, and membrane. Critical to this activity may be its function to autophosphorylate and thereby to persist in its “downstream” effects, even after the “upstream” event that initially stimulated it has waned. One of the most potent stimuli for its activation is Ca2+, and Wu and colleagues take advantage of this, using isoproterenol as an agonist to trigger Ca loading and potentiate the occurrence of arrhythmias. A critical and interesting part of the effect reported is that isoproterenol did not increase the frequency of early afterdepolarizations (EADs) in these mice, but did facilitate the occurrence of arrhythmia. The authors suggest that a lesion in the substrate induced the EADs, whereas a trigger mechanism brought on the arrhythmia. They present provocative evidence that the EADs themselves derive from activity at the level of the Na/Ca exchanger, and that ICa,L is at a higher baseline activity in the transgenic than wild-type mice and is more potently stimulated by isoproterenol (the trigger).

Hence, the arrhythmias in this model of hypertrophy appear dependent on a CaMKII-driven mechanism. Given the ubiquity of hypertrophy in so many settings that are arrhythmogenic, as well as the success of β-blockade in mitigating the consequences of cardiac disease and arrhythmia in diverse circumstances, there is the temptation to seek a target or targets within the CaM kinase II structure that would expand our library of drugs. Such a family of targets may turn out to be as valuable to us as those with which we have been familiarized thanks to research on the congenital long-QT syndrome. A caveat rests on whether in the absence of hypertrophy such targets will be equally applicable and therefore attractive. Even if applicability turns out to be limited to hypertrophy-associated arrhythmias, however, the value of the direction taken will still be immense, both for the identification and the exploration of new therapies.

A final thought derives from the continued debate over the value of mouse models in the study of human arrhythmias. Clearly, the mouse has an ECG that is repugnant to those of us who enjoy looking at T waves; indeed the mouse QRS-T complex is as truncated as some of the modified murine genes that are studied. Moreover, the ion channels determining repolarization differ, and even the mechanisms for arrhythmias may differ in mouse as compared with man. Nonetheless, the quality of thought going into work on these models and the clarity of understanding which results in many cases clearly augur well for the long-term upgrading of our therapeutic armamentarium, a point well-made in the current issue of the Circulation.

References


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