Interest in developing new antiarrhythmic drugs has vacillated between recession and eclipse since the CAST trial. This mind-set has been reinforced by additional studies of drugs (eg, SWORD) and of drugs versus devices (eg, AVID). A recent editorial and related publications focus on redefining the role of antiarrhythmic drugs, stressing a largely adjunctive strategy in which drugs are an accommodation of nonpharmacological therapies for ventricular arrhythmias. It is suggested that first-line drug therapy be reserved for arrhythmias like atrial fibrillation.

See page 2010

Is the future for pharmacological therapy of cardiac arrhythmias as bleak as it appears to be? Perhaps so, if we continue to define and develop antiarrhythmic drugs in a traditional sense as blockers of ion channels (Na, K, and Ca\(^{2+}\)) and/or adrenergic receptors. In this setting, we may expect continued refinement of decades-old thinking, perhaps more selective, more effective, and safer drugs, but hardly the stuff of which breakthroughs are made. Recent publications have stressed the need for alternatives to ion channel blocking drugs in the prevention and therapy of cardiac arrhythmias. These needs have arisen because 1) although often effective, ion channel blocking agents have not yet achieved sufficient target selectivity or sufficient safety to provide optimal intra- and interpatient treatment over extended periods of time, 2) the ability to prolong life and improve quality of life when these drugs are administered alone has been marginal, and 3) the recognition, through molecular and biophysical technology, of increasing arrays of potential molecular targets has not yet identified those targets that might be most beneficially modified, as well as practicable strategies that might be used to modify them. Perhaps most importantly, even if all the above concerns regarding ion channel blocking drugs are dealt with, we still are beset by an imperfect situation: imperfect because the prevention and treatment of most arrhythmias with ion channel blockers fails in so many instances to modify the root cause of the arrhythmia. Exceptions to this statement may be those arrhythmias that are traceable to genetically abnormal channels, as are seen in the congenital long-QT syndrome and Brugada’s syndrome, to name just two.

Why is the definition of antiarrhythmic drugs so fixated on agents that block or open ion channels? Is not any pharmacological approach, regardless of target, that prevents/terminates an arrhythmia antiarrhythmic? In fact, there are alternative pharmacological approaches to prevention and therapy that can be derived by moving “upstream” from the arrhythmia and its ion channel targets. This upstream approach likens present antiarrhythmic strategies and use of channel blockers to that of the little Dutch boy of fable who stuck his finger in a hole in a leaky dike and saved his village. When as a child I was told the story, I envisioned the leak stopping and the water rising, overflowing the dike and washing away boy, town, and wooden shoes. When one considers the results of EMIAT, in which antiarrhythmic mortality was reduced by amiodarone but overall mortality was not, then the analogy of being washed away—in this case by congestive failure—becomes ever more applicable. Is this the best we can hope for with pharmacological therapy of arrhythmias: plugging holes with channel blockers?

Upstream therapies do not uniquely ask how to plug the hole, but more importantly, how it got there—what is the cause of the arrhythmia, how can evolution of the substrate that produced the arrhythmia be stemmed or reversed, and/or what are the early warning signs of a deteriorating substrate that can focus us on preventing the initial expression of or the recurrence of the arrhythmia. Upstream therapies may be targeted not only at a substrate that has become arrhythmogenic but at a trigger that sets off the arrhythmia.

In light of this, Rahme et al take a welcome step, albeit not the first, in espousing a form of upstream therapy. Arguably the first such successful approach was the observation that \(\beta\)-adrenergic blocking agents reduced mortality postmyocardial infarction, later, that they prevented catecholamine-dependent or exercise-induced arrhythmias. Rahme et al report that a 5-HT\(_4\) receptor antagonist is antiarrhythmic in a swine model of atrial flutter or fibrillation. Given that knowledge of serotonin effects and serotonergic blockers has been with us for a while, one might question the novelty of Rahme et al’s observation. Novelty is seen in the successful targeting of the 5-HT\(_4\) receptor as the trigger mechanism in a model of clinically important arrhythmias. Within the context of the Sicilian Gambit discussion of arrhythmias, the 5-HT\(_4\) receptor would be a vulnerable parameter, a target whose modulation would alter expression of the arrhythmia. The 5-HT\(_4\) receptor would be a particularly attractive target in the human and the pig heart as it appears localized largely, if not totally, to the atrium. As such, it is reasonable to expect any agent that blocks the 5-HT\(_4\) receptor to have minimal untoward effects on ventricular function (unless, of course, it selects targets in addition to the 5-HT\(_4\) receptor).

Of major importance to the design of any upstream therapy is the demonstration that it modifies a process responsible for advancing the evolution of the arrhythmogenic substrate. Kaumann and Sanders, who have long championed the 5-HT story, suggested that for atrial fibrillation, exploitation of 5-HT\(_4\) receptor distribution would be a novel and potentially effective approach. The scenario they proposed recog-
nizes the damaging effects on endothelium of the hemodynamic dysfunction that accompanies both valvular and nonvalvular heart disease. They considered increasing atrial size and increasing age as factors that may lead to further endothelial damage, with attendant platelet aggregation resulting in 5-HT release. Given that 5-HT1 receptor activation triggers a signal transduction pathway not unlike that seen with β-1 adrenergic receptors (ie, a G protein-coupled increase in cAMP synthesis and elevation of intracellular calcium), the arrhythmogenic potential of the pathway is clear, and the expectation is that prevention of 5-HT1 receptor occupancy by its agonist might be antiarrhythmic.

Having said the above, it is clear that the study by Rahme et al—although demonstrating the antiarrhythmic efficacy of 5-HT1 receptor blockade—does not entirely address the hypothesis of Kaumann and Sanders. The anesthetized swine model in which fibrillation or flutter is induced by pacing and/or crush injury does not permit the requisite, chronically remodeling substrate associated with fibrillation to evolve. Nonetheless, given the combination of sewing an electrical array to the heart and crushing tissue while not reducing platelet aggregation, there is the possibility, even limited information available regarding the drug, questions depending on the answers to these questions, from an academic viewpoint the information can only be beneficial.

The above commentary does not demean the work by Rahme et al but is provided instead to highlight it within the context of what has been and needs to be done. Certainly direct testing of the Kaumann-Sanders hypothesis in appropriate arrhythmia models, including those in which fibrillation evolves over a period of time, would be of value. Third, the pathway subserved by the 5-HT4 receptor remains regarding its effects on other organ systems. Depending on the answers to these questions, an academic viewpoint the information can only be beneficial.

receptor blockers have the potential to become an attractive alternative to β-adrenergic and calcium channel blockers in the atrial fibrillation armamentarium. I state this for the obvious reason that if these preliminary observations are borne out, 5-HT1 receptor blockers would not manifest the negative inotropic action on the ventricle that characterizes β-adrenergic and calcium blockers. A positive result might also provide additional incentive to seek other upstream targets applicable to atrial fibrillation and flutter and to other arrhythmias, whether these targets are directly or indirectly involved in the evolution of the arrhythmogenic substrate. The potential of such targets has been recognized for some time. One example is the cardiac angiotensin II receptor system, which appears importantly involved in electrophysiological and structural remodeling of myocardium.

In closing, for the last 25 years we have seen attempts to prevent and treat arrhythmias focus on building a better amiodarone, still regrettably oversimplified by many as a class III antiarrhythmic. We also have seen additional variations on other ion-channel-blocking drugs, some more promising than others. But attempts to move significantly upstream have been modest, and—regardless of the fate of the particular drug studied—the work of Rahme et al sheds welcome light on the potential attractiveness of that direction.

References


**Key Words:** Editorials ■ antiarrhythmic agents ■ atrial fibrillation ■ serotonin
Leaky Dikes and Fibrillating Swine
Michael R. Rosen

Circulation. 1999;100:1942-1944
doi: 10.1161/01.CIR.100.19.1942

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/100/19/1942

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/