Interest in developing new antiarrhythmic drugs has vacillated between recession and eclipse since the CAST trial.1 This mind-set has been reinforced by additional studies of drugs (eg, SWORD2) and of drugs versus devices (eg, AVID3). A recent editorial4 and related publications5,6 focus on redefining the role of antiarrhythmic drugs, stressing a largely adjunctive strategy in which drugs are an accompaniment of nonpharmaceutical therapies for ventricular arrhythmias. It is suggested that first-line drug therapy be reserved for arrhythmias like atrial fibrillation.4

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 Ca2+) 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 breakthroughs are made. Recent publications7 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.8 Exceptions to this statement may be those arrhythmias that are traceable to genetically abnormal channels, as are seen in the congenital long-QT syndrome8 and Brugada’s syndrome,9 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.7 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,10 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 al11 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 β-adrenergic blocking agents reduced mortality postmyocardial infarction,12 and later, that they prevented catecholamine-dependent or exercise-induced arrhythmias.13,14 Rahme et al11 report that a 5-HT4 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,15–17 one might question the novelty of Rahme et al’s observation. Novelty is seen in the successful targeting of the 5-HT4 receptor as the trigger mechanism in a model of clinically important arrhythmias. Within the context of the Sicilian Gambit18 discussion of arrhythmias, the 5-HT4 receptor would be a vulnerable parameter, a target whose modulation would alter expression of the arrhythmia. The 5-HT4 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.19,20 As such, it is reasonable to expect any agent that blocks the 5-HT4 receptor to have minimal untoward effects on ventricular function (unless, of course, it selects targets in addition to the 5-HT4 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,21 who have long championed the 5-HT story, suggested that for atrial fibrillation, exploitation of 5-HT4 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-HT 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 calcium21), the arrhythmogenic potential of the pathway is clear, and the expectation is that prevention of 5-HT receptor occupancy by its agonist might be antiarrhythmic.

Having said the above, it is clear that the study by Rahme et al1—although demonstrating the antiarrhythmic efficacy of 5-HT receptor blockade—does not entirely address the hypothesis of Kaumann and Sanders.21 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 likelihood, of the occurrence of significant platelet aggregation and 5-HT release occurring in this model.

Rather than wax excessively enthusiastic over the availability of a selective 5-HT receptor blocker, we must note that very important questions remain. For example, could the 5-HT receptor blocker used by Rahme et al have ion channel-blocking or other effects in addition to its actions at the 5-HT receptor? If the drug had Ks-channel-blocking effects, then, on the basis of the cardiac distribution of Ks 22 these effects might be expressed far more at the level of atrium than ventricle and so could explain the electrophysiological findings. No cellular, electrophysiological, or ion channel studies are referred to in the paper or are presently available to the reviewer, and so this question must remain open-ended. Second, given the limited information available regarding the drug, questions remain regarding its effects on other organ systems. Depending on the spectrum of such effects, these could increase or decrease the desirability of developing and administering the drug. Third, the pathway subserved by the 5-HT receptor? If the drug had I Kur-blocking effects, then, on the particular drug studied—the work of Rahme et al sheds welcome light on the potential attractiveness of that direction.23


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Leaky Dikes and Fibrillating Swine
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