EDITORIAL COMMENT

Out With the Old and in With the New

Not So Fast in Hypertrophic Cardiomyopathy*

Martin S. Maron, MD

Over 50 years ago, Dr. Eugene Braunwald commenced the therapeutic era in hypertrophic cardiomyopathy (HCM) with the introduction of the beta-blocker propranolol. Over the last several decades, pharmacological intervention with beta-blockers or calcium-channel blockers continues to be the initial treatment for limiting heart failure symptoms due to left ventricular outflow tract obstruction (1). In 1985, the class IA antiarrhythmic drug disopyramide was also demonstrated to be effective and safe at lowering outflow gradients and improving heart failure symptoms, largely as a result of its negative inotropic properties. Although its use can be limited by parasympathetic side effects and limited long-term efficacy (2–5), North American and European expert consensus HCM guidelines have promoted disopyramide as an additional treatment option for symptomatic obstructive patients with HCM before considering highly effective invasive septal reduction therapy (6,7). However, despite the availability of disopyramide for over 35 years, the mechanism by which this drug provides the observed clinical benefit has not been well characterized in this complex heart disease, contributing to some apprehension and concern within the practicing cardiology community in recommending disopyramide therapy to patients with HCM (4,5).

In this issue of *JACC: Basic to Translational Science*, Coppini et al. (8) perform a number of elegant basic science experiments on isolated HCM cardiomyocytes derived from ventricular septal muscle obtained from obstructive patients with HCM at the time of surgical myectomy. A variety of effects of disopyramide were studied at the cellular level, including changes to ion fluxes, afterdepolarizations, and twitch tension. To relate these experimental findings to the clinical effect of disopyramide, electrocardiograms and echocardiograms were performed before and after 3 months of disopyramide therapy in a separate study cohort of 39 symptomatic obstructive patients with HCM.

At first glance, this investigation characterizing the mechanism of a drug that has been used clinically in HCM for some time could be inadvertently dismissed as old news. However, this is far from the reality because the basic and clinical observations derived from Coppini et al. (8) establish a number of principles that advance our understanding of an important therapy for controlling symptoms in patients with HCM and also provide an example for similar future initiatives in this disease.

One of the major observations derived from the extensive in vitro experiments performed in this study was the lack of a direct effect by disopyramide on the contractile apparatus of the heart. Instead, the substantial reduction (60%) in resting outflow tract gradient achieved with disopyramide was accomplished by altering myocardial contractile force by mitigating intracellular Ca^{2+} levels through direct action on multiple ion channels, including the peak and late Na channel current, the L-type Ca^{2+} current, and the ryanodine receptor (8). The negative

inotropic effect resulting from this alteration in cellular Ca^{2+} levels decreased early systolic flow acceleration enough to mitigate the abnormal hemodynamic drag forces that contribute to the mechanism of mitral valve–ventricular septal contact.

Of note, the impact of disopyramide on contractile force was associated with only a minimal decrease in ejection fraction (8). This is not a trivial issue because any intervention associated with a more significant decrease in systolic function would likely raise safety concerns, including potentially new heart failure symptoms resulting from diminished cardiac output. Therefore, these data by Coppini et al. (8), as well as prior prospective clinical studies with disopyramide (3,4,9), suggest that the minimal negative inotropic effect of disopyramide is not associated with increased risk. The excellent safety profile also results from the fact that disopyramide use resulted in only a very minimal increase in the corrected QT interval, an observation that further supports the growing practice of initiating disopyramide on an outpatient basis unless certain high-risk electrocardiographic features are present in a patient (4,8).

As the authors correctly point out, the mechanism of action of disopyramide in reducing outflow tract gradients contrasts sharply to the proposed mechanism of action of myosin inhibitors, an emerging novel class of drug therapy that is currently under evaluation in a number of clinical trials for the treatment of symptomatic obstructive HCM (10). The myosin inhibitors have been noted in early clinical investigations to lower gradients by producing a potent negative inotropic effect achieved by direct inhibition of cardiac myosin, with little off-target effect and an early acceptable safety profile (10). Although speculative at this point, the data by Coppini et al. (8) do raise the future prospect that outflow obstruction may be more effectively mitigated by using a therapeutic strategy utilizing the benefits of 2 drugs that lower gradient through different but potentially complementary (and hopefully synergistic) mechanisms. This is particularly relevant because treatment with disopyramide alone is associated with limited long-term efficacy in improving heart failure symptoms in an important subset of obstructive patients with HCM.

Coppini et al. (8) also establish rational for the observed safety and potentially beneficial antiarrhythmic effects of disopyramide in obstructive HCM. Early and delayed afterdepolarizations, a cellular trigger for arrhythmias, were noted to be decreased in HCM endocardial cardiomyocyte due to the effect of disopyramide on shortening the actional potential as well as decreasing the content of Ca^{2+} within the sarcoplasmic reticulum (8). Determining if the effects of disopyramide on early and delayed afterdepolarizations in human tissue culture translates into an actual decrease in clinical burden of atrial or ventricular arrhythmias in patients with HCM was not assessed in this study. Nevertheless, these rigorous basic science observations provide strong rational for future clinical investigations to determine the efficacy of disopyramide in reducing arrhythmic burden across the entire spectrum of patients with HCM, including patients without outflow tract obstruction.

An important issue not addressed by this investigation was clarifying the mechanism responsible for why close to one-third of obstructive patients with HCM do not achieve a significant decrease in outflow gradients (i.e., nonresponders) or why efficacy of the drug often diminishes over extend periods of time in other patients (3,4). Further work directed at identifying the cellular mechanisms responsible for these limitations of disopyramide would represent another critical next step forward for this translative science initiative, with the opportunity to potentially develop novel drug therapy specifically tailored to target all the basic mechanisms responsible generating outflow tract obstruction and in the process potentially further increase the number of drug therapy options available for patients with obstructive HCM.

Despite over 60 years since the first contemporary clinical descriptions of HCM (5), this genetic heart disease has been subjected to limited translational scientific investigation, a reason there has been no additional novel drug therapy for HCM since disopyramide. Coppini et al. (8) should be commended for a unique "bench to bedside" initiative in this complex, heterogenous genetic heart disease. By providing the basic mechanisms responsible for the observed clinical response of disopyramide in HCM, a large measure of reassurance has now been provided on the safety and efficacy of this drug to the practicing cardiology community and patients with HCM. Also, this translational study represents an important "call to arms" to the scientific community to continue to pursue investigation aimed at clarifying the basic mechanisms responsible for limiting symptoms in HCM and to identify novel therapeutic targets to further our treatment options for patients with this complex genetic heart disease, providing all HCM patients an even greater opportunity for improved quality of life.

ADDRESS FOR CORRESPONDENCE: Dr. Martin S. Maron, Hypertrophic Cardiomyopathy Center, Division of Cardiology, Tufts Medical Center, 800 Washington Street, #70, Boston, Massachusetts 02111. E-mail: mmaron@tuftsmedicalcenter.org.

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