Mechanism of Antiarrhythmic Effects of Flecainide in Catecholaminergic Polymorphic Ventricular Tachycardia

To the Editor:

We read with interest the recent article by Liu et al, in Circulation Research, on the mechanism underlying the antiarrhythmic effects of flecainide in catecholaminergic polymorphic ventricular tachycardia (CPVT).1 They conclude that Na+ channel block but not inhibition of the cardiac ryanodine receptor (RyR2) has a key role in the antiarrhythmic effects of flecainide in CPVT, because they found flecainide suppresses triggered activity without a reduction of Ca2+ waves in RyR2R4496C+/− mice. However, we have previously reported that flecainide directly inhibits RyR2 and thereby prevents CPVT.2 Evidence that flecainide reduces the frequency of triggered beats to a greater extent than that of spontaneous Ca2+ waves in cardiac calsequestrin Casq2 null (Casq2−/−) mice, another model of CPVT, led us to propose a dual mode of flecainide action in CPVT: suppression of spontaneous Ca2+ release from sarcoplasmic reticulum by RyR2 inhibition and suppression of triggered beats by Na+ channel block.2

Our studies with a range of sodium channel blockers support a role for RyR2 block in this setting. In our first report, we found that lidocaine, which does not inhibit RyR2, fails to suppress CPVT at a dose that produces similar Na+ channel block to a dose of flecainide that completely suppresses CPVT,2 which supports a direct role for RyR2 inhibition in this setting. The importance of RyR2 inhibition is further corroborated by our recent study, which tested the effects of all class I antiarrhythmic drugs clinically available in the United States in Casq2−/− mice.3 We found that RyR2 inhibition and Ca2+ wave suppression in vitro determined the antiarrhythmic efficacy against CPVT in vivo.3 The importance of RyR2 inhibition for preventing CPVT has also been confirmed by the recent report of the Chen group.4

One of the points of difference between the data of Liu et al and our work is the effect of flecainide on sarcoplasmic reticulum Ca2+ sparks: no apparent effect in RyR2R4496C+/− cells in the study by Liu et al5 and an increase in Ca2+ spark frequency and reduction of spark amplitude, width, and overall spark mass in mouse and rat myocytes in our studies.6,7 The discrepancy may relate to experimental conditions, because the basal Ca2+ spark frequency in the experiments by Liu et al is several fold higher than that of our experiments.1,5 If Ca2+ spark frequency is already very high, it may be difficult to detect any further increases caused by flecainide.

Another possible explanation for the reported discrepancy is that flecainide may be less effective against mutant RyR2R4496C+/− channels than wild-type RyR2 channels in the setting of Casq2 deletion. However, the Fishman group7 has reported that flecainide is effective in suppressing Ca2+ waves in Purkinje cells from the same RyR2R4496C+/− mouse model studied by Liu et al. Furthermore, we reported that flecainide and propafenone (which also blocks RyR2 channels) were effective in CPVT patients carrying mutations in RyR2,8,9 whereas other sodium channel blockers that did not inhibit RyR2 in our experiments were ineffective in CPVT patients.8–10 Taken together, these clinical and experimental findings suggest that both Na+ channel block and RyR2 inhibition are important for the antiarrhythmic effects of flecainide in CPVT. The interesting results reported by Liu et al1 show that more experiments are needed to fully define the mechanisms of drug action in CPVT patients.

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Disclosures

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