Ionic and Cellular Mechanisms Underlying the Development of Acquired Brugada Syndrome in Patients Treated with Antidepressants

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Background: Tricyclic antidepressants, such as amitriptyline, is reported to induce ST segment elevation in the right precordial ECG leads, thus unmasking Brugada syndrome (BrS). The mechanism by which antidepressants induce the BrS phenotype and associated sudden death is not well established. Methods and Results: Action potentials (AP) were recorded from epicardial and endocardial sites of coronary-perfused canine right ventricular wedge preparations, together with a transmural pseudo-ECG. Amitriptyline alone (0.2 μM-1 mM) failed to induce a BrS phenotype. In the presence of NS5806 (8 μM), a transient outward potassium channel current (Ito) agonist, a therapeutic concentration of amitriptyline (0.2 μM) accentuated the epicardial AP notch leading to ST-segment elevation of the ECG. All-or-none repolarization at some epicardial sites but not others gave rise to phase-2-reentry and polymorphic ventricular tachycardia (VT) in 6 of 9 preparations. Isoproterenol (100nM) or quinidine (10 μM) reversed the effects of amitriptyline. Using voltage-clamp techniques applied to isolated cardiomyocytes, 0.2 μM amitriptyline was shown to produce use-dependent inhibition of sodium channel current (I Na), without significantly affecting Ito (n=5). Conclusions: Our data suggest that amitriptyline-induced inhibition of I Na unmasks the Brugada ECG phenotype and facilitates development of an arrhythmogenic substrate only in the setting of a genetic predisposition by creating repolarization heterogeneities that give rise to phase-2-reentry and VT. Keywords: cardiac arrhythmias, sudden cardiac death, amitriptyline