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Cellular and ionic mechanisms underlying effects of Cilostazol, Milrinone and Isoproterenol to suppress Arrhythmogenesis in an experimental model of early repolarization syndrome

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Background: Early repolarization syndrome (ERS) is associated with polymorphic ventricular tachycardia (PVT) and ventricular fibrillation (VF), leading to sudden cardiac death.

Objective: The present study tests the hypothesis that the Ito-blocking effect of phosphodiesterase-3 (PDE-3) inhibitors plays a role in reversing repolarization heterogeneities responsible for arrhythmogenesis in experimental models of ERS.

Methods & Results: Transmembrane action potentials (AP) were simultaneously recorded from epicardial and endocardial regions of coronary-perfused canine left-ventricular (LV) wedge preparations, together with a transmural pseudo-ECG. The Ito-agonist NS5806 (7-15 μM) and ICa-blocker verapamil (2-3 uM) were used to induce an ER pattern and PVT. Following stable induction of arrhythmogenesis, the PDE-3 inhibitors Cilostazol and Milrinone or Isoproterenol were added to the coronary perfusate. All were effective in restoring the AP dome in the LV epicardium, thus abolishing the repolarization defects responsible for phase-2-reentry (P2R) and PVT. Arrhythmic activity was suppressed in 7/8 preparations by Cilostazol (10 μM), 6/7 by milrinone (2.5 μM) and 7/8 by isoproterenol (0.1-1 μM). Using voltage clamp techniques applied to LV epicardial myocytes, both Cilostazol (10 μM) and milrinone (2.5 μM) were found to reduce Ito by 44.4% and 40.4%, respectively, in addition to their effects to augment ICa.

Conclusions: Our findings suggest that PDE-3 inhibitors exert an ameliorative effect in the setting of ERS by producing an inward shift in the balance of current in the early phases of the epicardial AP via inhibition of Ito as well as augmentation of ICa, thus reversing the repolarization defects underlying development of P2R and VT/VF.

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