# Role of the Late Sodium Current in Arrhythmias Related to Low Repolarization Reserve

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A hallmark of long QT syndrome is the prolongation of action potential duration (APD), which can be related to conditions of low repolarization reserve. An unbalance between depolarizing and repolarizing currents can fire early after depolarizations (EADs), precursor for the polymorphic ventricular tachycardia called Torsade de Pointes (TdP). This repolarizing disorder has been observed under pathological situations, such as heart failure (HF), oxidative stress, ventricular hypertrophy and/or in the presence of pure class III antiarrhythmics. Under such circumstances, there is evidence that the alteration of the late sodium current (INaL) has an important role.

The goal of this study is to evaluate the effects of INaL enhancement in the different cells of the ventricular wall under normal conditions and to analyze the role of INaL under pathological conditions prone to EADs generation. A formulation of human INaL was introduced in ten Tussher AP model, and the effects on APD and APD rate-dependency were evaluated. Simulations of EADs were also conducted under low repolarization reserve conditions.

Our results show that the increase in the maximum conductance of INaL prolongs APD in a rate-dependent manner, in agreement with experimental studies. A 10-fold increase of INaL prolongs APD in 35 %, 44 % and 80 % for a stimulation rate of 1 Hz in endocardial, epicardial and M cells, respectively. Additionally, APD rate-dependence was more pronounced in M cells (APDMax (0.5 Hz) -APDMin (0.33 Hz) yielded 123 ms versus 42 ms and 92 ms in epicardium and endocardium, respectively ), especially when INaL was enhanced. Finally, the enhancement of INaL under conditions of low repolarization reserve led to EADs formation in M cells.

In conclusion, INaL enhancement is proarrhythmic in M cells with low repolarization reserve and under pathologic conditions prone to EAD generation.