

Action Potential and QT Prolongation Not Sufficient to Cause Torsade de Pointes: Role of Action Potential Triangulation

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Editorial Comment

Syncope and sudden death resulting from Torsade de Pointes (TdP) are very uncommon but major adverse drug effects. Prolongation of the QT interval is the most widely used marker of this potential. Minimal prolongation of the QT interval has been the basis for termination of drug development programs, the imposition of significant restrictions on prescription or withdrawal of drugs from the market. In the absence of drug treatment or electrolyte abnormality, QT interval prolongation is a common finding in clinical electrocardiography. In this setting, syncope and sudden death are largely restricted to individuals with inherited mutations of cardiac ion channel genes. Roden¹ and Hondeghem² have summarized compelling arguments that simple QT interval prolongation is a poor marker for proarrhythmic susceptibility. The many shortcomings of the long QT-proarrhythmia hypothesis include:

1. Drugs that produce the same QT interval prolongation do not pose equivalent proarrhythmic risk. Proarrhythmia is rare with amiodarone treatment, but common with quinidine. The QT interval is normal in a majority of patients in some series of drug-induced proarrhythmia.
2. Among the congenital syndromes associated with abnormal repolarization, the *short* QT syndrome poses the greatest risk.

Hondeghem and colleagues have proposed a constellation of signs—Triangulation, Reverse use dependence, electrical Instability, and Dispersion (TRiAD)—as the predictors drug-induced proarrhythmia.²⁻⁴ Triangulation defines a change in action potential (AP) shape as a result of slowing of repolarization with the APD₃₀ to APD₉₀ increased. Triangulation may be accompanied by either shortening or lengthening of the total action potential duration. Reverse use-dependence describes a pattern of ion channel blockade in which greater block is observed at slow heart rates. It is the characteristic pattern of drug-induced blockade of the delayed rectifier potassium current, I_{Kr}. Reverse use-dependence is associated with a steep QT-RR interval relationship with a positive slope. This steep slope results in significant beat-to-beat instability of the action potential duration (APD). This instability is more predictive of TdP than QT prolongation. The small stochastic variations in membrane currents become exaggerated, and marked APD variations between regions result in

APD dispersion. The instability and spatial dispersion are the basis for chaotic behavior.

The Hondeghem group used an in vitro rabbit heart model (SCREENIT) to test the predictive accuracy of TRiAD to identify potentially proarrhythmic drugs (reviewed in Ref. [4]). Triangulation, reverse use-dependence and an instability index were determined from monophasic action potentials recorded from isolated perfused rabbit hearts. SCREENIT was validated with 31 coded prototype drugs in a blinded fashion. Drugs known to be proarrhythmic by clinical or other experiences were correctly identified. Drugs with low proarrhythmic potential were also appropriately classified.¹ The potential value of TRiAD was largely substantiated in more than 700 trial drugs.⁴

The formulation of TRiAD as a basis for identifying proarrhythmic potential was largely empiric. Providing a hypothesis for the predictive value of TRiAD is challenging. Post-pause early after-depolarizations (EADs) are the most widely accepted basis for the initiation of TdP. The central question is the role of one or more features of TRiAD in the generation of EADs. Much theoretical and experimental work has been performed on the ionic basis of EADs.⁵⁻⁷ January and Riddle have proposed two phases for the formation of EADs: an initiation or conditioning phase that leads into a depolarization phase. The ion channel and pump currents that control the action potential shape are responsible for the conditioning phase. Reactivation of I_{Ca2+L} is crucial to the depolarizing phase of EADs.^{2,6} The figure illustrates the normal and post-pause action potential, [Ca²⁺]_i, fractional availability of the calcium channel, f^{*}f_{ca}, and the calcium current. We simulate a case in which the AP was made more triangular by increasing I_{Kur}, but producing little change in the overall APD. The 40th beat of a 2 Hz train and a post-pause AP are illustrated. Triangulation is associated with a negative shift in the plateau potential. The post-pause AP shows oscillations at the plateau level of membrane potential. As illustrated in Figure 1C, the triangulation of the AP is associated with greater recovery of I_{Ca2+L}. Reduction of the maximal calcium conductance abbreviates the AP and abolishes the oscillations. Therefore, changes in action potential shape that may be a basis for reactivation of the calcium current that favors the development of TdP.

In this issue of the *Journal*, Guo et al.⁸ present the result of an elegant series of experiments designed to identify a basis for the role of triangulation in the genesis of EADs. They used ventricular myocytes from rabbit and guinea pig hearts. Rabbit ventricular myocytes have a triangular shape with shallow phase-two and -three slopes. Guinea pig ventricular myocytes have a rectangular action potential with phase two maintained at depolarized levels, followed by a rapid phase three. They show that only rabbit ventricular myocytes generate EADs when exposed to 0.01 μM dofetilide;

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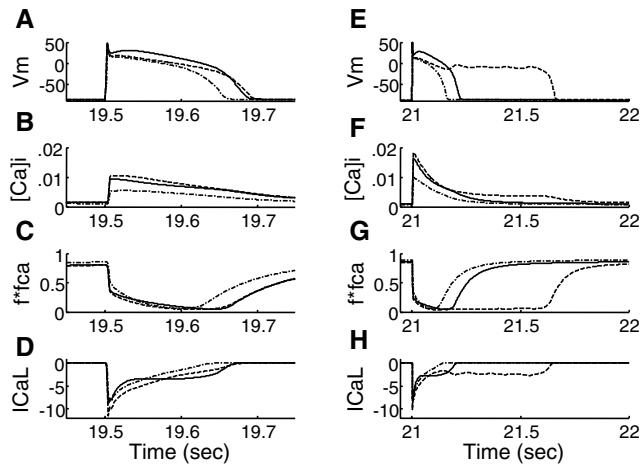


Figure 1. The 40th beat of a 2 Hz action potential train (Panels A-D) and the first post-pause action potential (Panels E-F) were simulated using the Luo-Rudy action potential model. The simulations for the normal case are shown in black; the triangulated action potential case in blue; the case after a reduction of the maximal calcium channel conductance in red. V_m \equiv membrane potential, panels A and E; $[Ca^{2+}]_i$ \equiv the intracellular calcium concentration, panels B and F; $f \cdot f_{Ca}$ \equiv the fractional availability of the calcium current, panels C and G and I_{CaL} \equiv the calcium current, panels D and H. See text for further discussion.

guinea pig ventricular myocytes do not. In a creative part of the experiment design, they showed that reactivation of I_{CaL} is accelerated when guinea pig or rabbit myocyte is voltage clamped using the rabbit action potential as the voltage command, but not with the guinea pig action potential. In other words, the faster reactivation and presumably the susceptibility to TdP are the result of the change in action potential shape. The study of Guo et al.⁸ provides a basis for the empiric observation of the role of the action potential shape in the development of TdP.

The study of Guo et al.⁸ provides a perspective on the consequences of triangulation. It did not examine the possible mechanisms of the AP triangulation. This will require examination of the channel and pump currents that control phases two and three of the action potential. The study also suggests a possible mechanism by which disease states such as ventricular hypertrophy and heart failure, which change the action potential shape, may be proarrhythmic. Although the studies were performed on guinea pig and rabbit ventricular myocytes, we believe the conclusion may be valid in man. Induction of EADs was more dependent on AP shape than on species.

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