Elucidation of mechanisms that trigger torsades de pointes in drug-induced long QT syndrome: a simulation study

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Abnormalities of action potential (AP) in cardiomyocytes and of AP propagation lead to cardiac arrhythmias. It is believed that early afterdepolarization (EAD) which is a transient depolarization during the AP repolarization phase triggers fatal arrhythmias such as Torsades de Pointes (TdP) in drug-induced long QT syndrome (diLQTS). However, the EAD-mediated arrhythmogenic mechanism in the ventricle is not fully understood. In the present study, we investigated how the numbers and locations of myocardial units evoking EAD in the myocardial tissue related to arrhythmogenesis. To examine how EADs locally evoked in ventricular tissues lead to arrhythmias, we constructed a mono-domain myocardial sheet model (6 cm × 6 cm) consisting of 360,000 human ventricular myocardial units. Each ventricular unit was represented by a human ventricular myocyte model developed by Kurata *et al* (2005). We performed computer simulations of AP propagation, assuming the bradycardia (0.5-Hz pacing) and administration of class III anti-arrhythmic agents. Spiral wave-like excitations, i.e., reentrant arrhythmias, occurred only when EAD-forming units were located at the center of the myocardial sheet as a square area and occupied 80–90% of the myocardial sheet area. On the other hand, we found that when the EAD-forming unit areas (EAD clusters) were discontinuously distributed in the myocardial sheet, the reentrant arrhythmias can be triggered with fewer EAD-forming units (30–40% of the total myocyte units). These results suggested that not only the number of myocytes generating EADs coordinately but also the location of EAD-forming units is involved in fatal arrhythmia onsets.