Early Afterdepolarizations, U Waves, and Torsades de Pointes

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Torsades de pointes (TdP) is defined as a polymorphic ventricular tachycardia (VT) with a twisting QRS morphology associated with a prolonged QT interval and/or increased U wave amplitude in the ECG. Patients with acquired or congenital long-QT syndrome (LQTS) can develop TdP that results in sudden cardiac death. Fifty or more drugs, both typical antiarrhythmic agents such as quinidine as well as other classes of drugs such as some antibiotics, affect membrane ionic currents, prolong the duration of the QT interval in the ECG, and have been associated with the acquired LQTS. Similarly, inherited genetic defects in the cardiac membrane ion channels can cause congenital LQTS. Some patients with apparent acquired LQTS may actually have mild congenital forms and remain asymptomatic until exposed to one of the drugs noted above. Congenital LQTS can be divided into multiple subtypes depending on the affected membrane ionic currents (eg, LQT1, LQT2, and LQT3 for alterations in $I_{Ks}$, $I_{Kr}$, and the inactivation process of $I_{Ks}$). Due to the possible fatal outcome and involvement of many drugs, it is important to understand the mechanism of TdP, predict its occurrence, and manage it clinically.

Mechanism

It has been suggested that an early afterdepolarization (EAD) exceeding the activation threshold, arising from the endocardium (including the Purkinje network) or from the midmyocardial region, could initiate TdP. EADs have been observed experimentally in monophasic action potential recordings at multiple epicardial and endocardial sites. Increased dispersion of repolarization preceding the TdP induction has been noted in an isolated rabbit heart model of LQT2. Long intervals between activations, ie, slow rates, prolong the duration of the action potential and increase the transmural dispersion of repolarization. An action potential with a long duration increases intracellular Ca$^{2+}$ concentration that promotes membrane potential oscillations and formation of EADs in isolated Purkinje fibers and in isolated cells from mid-myocardial (M) cells. It has also been suggested that TdP can be initiated by delayed afterdepolarizations (DADs) or by reentry following premature epicardial stimulation that caused unidirectional conduction block within the large area of repolarization dispersion. The subsequent beats of TdP could be maintained by either reentry or new focal activation initiated at one or multiple sites. However, the existing experimental support for the above hypotheses is limited, and lack of knowing a precise mechanism has hampered our ability to predict and manage TdP clinically.

U Wave

Einthoven designated the U wave in the ECG almost a century ago. However, its origin and clinical significance are still debated. Three hypotheses have been proposed to explain its occurrence. The first is that repolarization of Purkinje fibers could cause the U wave, because they were temporally related. However, the small mass of Purkinje fibers, in relation to the very large mass of ventricle, may be insufficient to affect the ECG and generate the U wave. It was observed that the U wave in the ECG occurred at the same time as the EAD recorded in a monophasic action potential from the endocardium of a patient with quinidine-induced LQTS and TdP. Nevertheless, it was argued that mid-myocardial cells (M cells) with long action potential durations (APD) could produce a hump at the end of the endocardial monophasic action potential similar to the waveform of an EAD. More recently, it was suggested that the long APD of M cells could divide the T wave into 2 sections, forming the T wave and the U wave. The M cell hypothesis is attractive because U waves obviously occur in normal individuals, as do M cells. The EAD explanation would require postulating the presence of low-amplitude or nonpathological EADs in these normal people. However, the M cell hypothesis has been challenged because it was shown that the dispersion of APD in the intact ventricle was much less than in isolated ventricular cells, due to the strong electrotonic interactions through the gap junctions in cardiac muscle. It was postulated that the reduced dispersion of APD in intact ventricular muscle decreased the possibility of M cells creating the U wave. Thus, the issue is still not resolved. Clinical observations add to the confusion of the origin of the U wave somewhat because negative U waves have been noted in patients with significant left ventricular ischemia and left ventricular hypertrophy and are also inadequately explained.

U to T Ratio

In the present issue of Circulation, Gbadebo et al demonstrate that the ratio of U wave to T wave amplitude (UTA) can be used as an ECG parameter to predict the initiation of TdP. They observed in a rabbit LQT2 model, created by using methoxamine to slow the heart rate and decrease outward potassium currents ($I_{m}$, $I_{Ks}$, and $I_{ACD}$) and clofilium to reduce $I_{Ks}$, a progressive and significant increase in UTA prior to the onset of TdP in control animals. Those animals treated with the calmodulin inhibitor, W-7, had suppression of both TdP and the U wave without affecting the QT interval. Therefore, both TdP and U wave were calmodulin-dependent. Previous
studies from the same research group demonstrated in the rabbit LQT2 model that calmodulin kinase augmented cardiac L-type Ca\(^{2+}\) current and the resulting EAD caused TdP,\(^{19}\) which was prevented by the calmodulin antagonist, W-7.\(^ {20}\) By using W-7, they essentially blocked the signal transduction pathway between LQT and L-type Ca\(^{2+}\) current, and therefore prevented EADs. It would be interesting to study further the effects of W-7 on isolated cells from epicardium, mid-myocardium, endocardium, and Purkinje fibers because M cells and Purkinje fibers may be more likely to generate EADs than cells from the epicardium or endocardium.

Although the U wave was in the original definition of TdP, the mechanistic relationship between the U wave and TdP is unclear because of multiple competing hypotheses for the origin of U wave as well as for the initiation of TdP, as noted. Clinical examples of a large U wave preceding the onset of TdP certainly suggest at least a temporal relationship between the two.\(^ {20}\) We also know that T wave alternans (TWA) can identify hearts at increased risk of TdP and can lead to prevention therapies. How- ever, it is important to remember that not all drug-induced proarrhythmia is from TdP. Other mechanisms play a role, as we learned from the Cardiac Arrhythmia Suppression Trial. Using the calmodulin inhibitor to reduce EADs also suggests a possible clinical strategy for the management of congenital LQTS. However, further studies on W-7 and other similar calmodulin inhibitors are needed to define their physiological effects and to evaluate their potential for treating patients with congenital LQTS. Also, whether the UTA is useful clinically needs to be established. Nevertheless, to be able to predict the onset of TdP by using the U wave could have significant clinical potential in identifying patients at increased risk of TdP and can lead to prevention therapies.

Finally, we need to remember that, as all proarrhythmia events are not due to TdP, it is also probable that some TdPs may not be predicted by the U wave criterion. For example, to propose an EAD origin of the U wave would require that the EAD arose in a significant volume of ventricular muscle to be registered in the ECG. If it began in Purkinje fibers, it might not be recognized electrocardiographically, as mentioned earlier. However, EADs arising in Purkinje fibers could conduct to ventricular muscle and still be capable of initiating TdP. Similarly, the U wave criterion may not predict TdPs that result from DADs or reentry. The value of the U wave in TdP prediction should also be evaluated in other animal species and in LQTS models created by methods other than the combination of methoxamine and clofilium that was used by Gbadebo et al.\(^ {18}\)

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**References**

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