Electrophysiological Mechanisms for Digitalis Arrhythmias

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ONE OF the most serious manifestations of digitalis intoxication is digitalis arrhythmia. The mechanism of the generation of arrhythmias by digitalis has interested many pharmacologists and physiologists who have pointed out several electrophysiological effects caused by digitalis. They are:

1. The increase in automaticity in the Purkinje fiber with concomitant depolarization of the membrane.
2. The depression of the atroventricular conductivity and impulse generation in the sinoatrial node by direct effects on the nodes or by indirectly stimulating vagal activity or antagonizing sympathetic activity.
3. The stimulation of central sympathetic centers.

These digitalis-induced effects may suppress supraventricular control while enhancing ventricular automaticity, resulting in the generation of ventricular tachycardia. However, such electrophysiological properties cannot explain the following findings.

1. The most common form of digitalis-induced ventricular tachycardia is bigeminy, and these closely coupled extra beats are now more easily explained by re-entry mechanism.
2. Electrical shocks or stimuli often induce ventricular tachycardia during digitalis administration. This phenomenon, called repetitive ventricular response or overdrive enhancement of automaticity, is different from the behavior of normal automaticity which is suppressed after rapid driving.

The question whether the repetitive ventricular response observed in the in situ heart is due to

re-entry excitation or abnormal automaticity can be studied electrophysiologically using the isolated cardiac tissues. The frequency dependent increase in automaticity was observed using canine Purkinje fibers. But the demonstration by Ferrier et al., Saunders et al., Hashimoto and Moe and Rosen et al. of "transient depolarization" and "low amplitude potential" clarified that digitalis induces abnormal automaticity which is enhanced by rapid driving and that this digitalis-induced automaticity can elicit coupled extra beats without a re-entry mechanism.

Transient depolarization

Transient depolarization is a hump-like small depolarization following repolarization of action potential as shown in Fig. 1. This potential change was produced by acetylcholine (a semi-synthetic aglycone) or ouabain, but normally obscured by the subsequent electrically driven action potential when constant driving is applied to the preparation. However, when I or 2 seconds of rest are interposed between trains of stimulation, transient depolarization can be observed, as shown in Fig. 1.

The characteristics of transient depolarizations are as follows.

1. Transient depolarization (TD) consists of two depolarizations (TD-1 and TD-2).
2. TD-1 has almost the same coupling interval as the preceding driving interval, when the coupling interval is measured from the rising phase of the action potential to the peak of TD. TD-2 has a coupling interval that is almost twice the preceding driving interval.
3. Both TD-1 and TD-2 can reach threshold and produce propagated action poten-

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Fig. 1. Transient depolarization in Purkinje fiber. Upper tracing: intracellular potential recording, lower tracing: stimulation pattern. AS = acetylstrophanthidin.
(From HASHIMOTO and MOE, Circ. Res. 32: 618, 1973, with permission)

(4) The amplitude of the TD changes with the preceding driving interval. The amplitude of TD-2 increases as the preceding driving interval shortens, i.e., rapid driving can increase the amplitude of TD and increase the incidence of reaching threshold to induce coupled ectopic beats.\(^{16}\)

(5) TD appears when spontaneous automaticity of the ventricular Purkinje fiber is suppressed.\(^{16}\)

(6) TD appears when the membrane potential is not markedly depolarized.\(^{16,18}\)

(7) TD can be observed not only in ventricular Purkinje fiber, but also in atrial plateau fiber.\(^{18}\)

(8) TD usually does not occur in the atrial and ventricular muscle fibers.\(^{16-18}\)

(9) TD induces functional conduction block in Purkinje fibers by decreasing electrical excitability at the peak of depolarization.\(^{17}\)

These properties may be responsible for the generation of ectopic beats by overdriving or premature extrastimulation and also for bigeminy or trigeminy and ventricular tachycardia during digitalis toxicity. An especially important finding is that the TD can produce functional block which is necessary for the TD to be an ectopic focus, because the coupling interval is equal or longer than the preceding cycle length. This importance of block for the ectopic pacemaker whose intrinsic rate is slow is described by Mendez and Moe.\(^{9}\)

**Electrophysiological mechanisms for the late phase of digitalis toxicity**

TD is a phenomenon which explains the generation of arrhythmias during the especially early phases of digitalis toxicity.\(^{20}\) However the effect of digitalis in increasing ventricular automaticity was also observed in our experiments by raising the dose of acetylstrophanthidin.\(^{18,21}\) This increase in spontaneous automaticity in the isolated Purkinje fiber followed the phase of depressed automaticity with occurrence of TD,
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Fig. 2. Correlation between the dose of digitalis, arrhythmias and cellular mechanisms.
ion=inotropic, RVR=repetitive ventricular response, Exs=extrasystoles, BG=begeminy, VT=ventricular tachycardia, VF=ventricular fibrillation, TD=transient depolarization, Autom=spontaneous automaticity, Cond V=conduction velocity, PM Block=Purkinje to muscle block.

similar to the automaticity observed in the blood-perfused canine ventricular automaticity.\(^{22}\) This increased automaticity occurs at the voltage level of nearly -60 mV, which is more depolarized than the voltage level for TD. For this automaticity, electrical stimulation could not accelerate the rate.

As the toxicity progressed, not only increases in spontaneous automaticity but also various conduction disturbances were observed.

1. In papillary muscle preparations with attaching free running Purkinje fiber, acetylchrophathidin in moderate and high doses blocked orthodynamic conduction, i.e. from Purkinje to muscle conduction, while antidromic conduction, muscle to Purkinje conduction, was maintained. This one way block is a favorable condition for induction of re-entry excitation of closely coupled extrasystoles.\(^{21}\)

2. Intraventricular conduction, examined using long false tendon, was also depressed by digitalis. Using lower doses of acetylstrophathidin to induce TD in 4 mM potassium Tyrode solution, decreasing potassium concentration resulted in decreased conduction velocity without concomitant decrease in maximum dV/dt. Later very slow conduction similar to that observed in very high potassium concentration was observed and finally inexcitability developed. These disturbances of conduction and increases in spontaneous automaticity produced by digitalis may be the mechanisms responsible for the ventricular tachycardia or fibrillation observed in the final stage of digitalis intoxication.\(^{23}\)

Fig. 2 summarizes the correlation between the dose of digitalis, arrhythmias and cellular changes.

**Ionic mechanisms for digitalis-induced electrophysiological changes**

Transient depolarization is an abnormal automaticity which is enhanced by rapid driving and thus different from normal phase 4 depolarization. This kind of automaticity has also been observed using norepinephrine\(^{24}\) and probably aconitine\(^{25}\) and veratrine\(^{26}\) induce similar automaticity. Whether all of these abnormal automaticities have similar ionic mechanisms has not yet been clarified. Transient depolarization observed in atrial and ventricular specialized tissue is depressed by high K concentration\(^{18,27}\) and that of atrial tissue is depressed by acetylcholine\(^{18}\). These findings suggest that the K ion or K current may have an important role in the generation of transient depolarization. Transient depolarization is one of the after-potentials or oscillatory changes in membrane potential, and Hauswirth et al.\(^{28}\) analysing ionic mechanisms for oscillation reported that voltage and time dependent changes in \(i_{K4}\) current (mainly carried by K) is responsible. However digitalis-induced transient depolarization occurs without much
depolarization of the membrane as compared to oscillation, which occurs at the membrane potential range around −70 to −60 mV. Thus, the \(i_{K1}\) current is not activated and cannot play a significant role in the generation of transient depolarization.

Ferrier and Moe\(^7\) demonstrated that Ca current may be important. They showed that transient depolarization is suppressed by lowering extracellular Ca concentration or by using the Mn ion. Whether the Mn ion suppresses not only the slow inward current (mainly carried by Ca) but also the Ca movement at the early diastolic phase must be clarified, these observations indicate the important role of the Ca ion in the generation of transient depolarization. This hypothesis is attractive because transient depolarization is similar to the digitalis-induced aftercontraction, in which case intracellular Ca movement must have occurred.\(^{29}\) However, Ca, Mn or so-called Ca antagonists have recently been shown not only to alter the slow inward current, but also to alter the slow K current (\(i_{K}\))\(^{30}\) The voltage clamp experiment is one method for studying the problem of which, the K current or the Ca current, is the primary mechanism for generation of transient depolarization.

Voltage clamp experiments on ventricular tissue have been reported, but so far not clear answer has been given for the mechanism of transient depolarization. Decrease in the slow inward current and decrease in the outward current has been reported and these findings may explain the lengthening of action potential duration in the early phase of digitalis effects.\(^{31}\) Decrease in the pacemaker current (\(i_{K2}\)) with increase in the background inward current explain increased spontaneous automaticity in the late phase of digitalis toxicity.\(^{32}\) At this toxic phase of digitalis, Na+, K- ATPase inhibition and resulting K loss from the cell may also explain the changes in membrane resistance and decreased excitability. These changes in automaticity and conduction may be the mechanism for the final stage of digitalis arrhythmias.

Unfortunately there has as yet not been clear cut data to explain the generation of transient depolarization. This phenomenon is an early changes in digitalis toxicity, and probably the most important mechanism for clinically observed arrhythmias. It is expected that if the mechanism for and the effects of antiarrhythmic drugs on the transient depolarization are clarified, a more rational use of digitalis or treatment for digitalis intoxication will become possible.

REFERENCES


