Digitalis Cardiotoxicity

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Clinical manifestations of digitalis toxicity were clearly described by Withering in 1785. One hundred years later, certain digitalis-induced arrhythmias were inscribed on the smoked drum, and shortly thereafter with the introduction of the electrocardiograph, manifestations of digitalis toxicity as recognized today were recorded in animals and human beings.

With popularization of the direct-writing electrocardiograph in the late 1940s and the introduction of digitoxin in recommended doses (that in retrospect appear inappropriately high), the documented prevalence of digitalis toxicity increased rapidly. With increased understanding of the interaction of electrolytes and digitalis and perhaps, and more importantly, the widespread use of digoxin in doses derived largely from its inotropic action and, thus, inappropriately low for the management of many of the arrhythmias, the prevalence of digitalis toxicity began to decline again. In addition, the advent of serum level determinations and the widespread acceptance of the concept of "therapeutic" levels which, although frequently falling short of the desired clinical end point, served to preclude digitalis toxicity.

With the decline in the incidence of digitalis toxicity consequent to these factors, some of the digitalis-related arrhythmias that were common are now rarely observed. This report focuses on arrhythmias that are highly specific for digitalis toxicity and on those that now are less commonly encountered. The discussion and classification of the arrhythmias are based on their most probable electrophysiologic mechanism.

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Historical Background

Two hundred years ago, Withering (1) wrote, "The foxglove when given in large doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motion to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death." While describing the protean nature of digitalis intoxication, he pointed to cardiotoxicity as the cause of death. For an interesting and detailed review of the history of digitalis toxicity the reader is referred to the text by Scherf and Schott (2). According to these authors, the earliest reports of experimentally and clinically induced cardiotoxicity are probably those of Boelus and Ferriar. In 1872, Boelus administered digitalis to frogs and wrote, "[the] diastolic part of the wave was interrupted half-way by rudimentary second systole." Ferriar, in 1799, administered digitalis to a patient with tuberculosis and the medication "was not suspended till the pulse was disposed to intermit, and some degree of nausea was excited (the intermission was not the effect of sickness)." In 1910, Rothberger and Winterberg (3) first published a systematic electrocardiographic study of digitalis-induced arrhythmias in the dog. There are a number of recent comprehensive reviews on digitalis cardiotoxicity (4-11).

The cellular and extracellular bases for digitalis toxicity and the factors that alter the sensitivity of the heart to digitalis are dealt with elsewhere in this symposium. In this report, we will discuss the electrocardiographic manifestation of digitalis toxicity in human beings, focusing on arrhythmias with a high degree of specificity for digitalis toxicity and especially on once common arrhythmias and selected electrophysiologic manifestations of cardiotoxicity which are now much less frequent because of a significant decline in the incidence of digitalis toxicity.

Diagnosis of digitalis cardiotoxicity is difficult and requires a careful correlation of the electrocardiographic findings with all available clinical and laboratory information. In addition, with rare exception, arrhythmias identical to those induced by digitalis also may be a manifestation of the basic underlying myocardial disease or a variety of ex-
tracardiac factors, or both. In fact, at times, digitalis cardiotoxicity may not be clinically evident, remaining "concealed" or "masked" until the dominant rhythm is slowed, allowing an accelerated subsidiary focus to become manifest (5). Such masked toxicity is a particularly interesting phenomenon complicating the diagnosis of digitalis intoxication (Fig. 1).

The incidence of the diverse manifestations of digitalis-induced cardiotoxicity is difficult to estimate. The retrospective nature of the studies, the lack of specificity of most arrhythmias for digitalis toxicity, differences in perception of toxicity by different investigators and, most importantly, the lack of a reference standard with which electrocardiographic manifestations of suspected toxicity can be compared compound the problem. In a prospective study (12) designed to deliberately induce digitalis toxicity, 20 of 39 patients were thought to manifest cardiotoxicity. The manifestations included premature ventricular complexes in 15 patients, sinus bradycardia with junctional escape in 11, ventricular bigeminy in 8, atrial fibrillation in 6, atrial tachycardia with block in 5, atrial tachycardia without block in 3, second degree atrioventricular (AV) block in 5 and atrial premature complexes in 2. Despite the prospective nature of the study, however, it is not certain that all the arrhythmias were caused by digitalis intoxication. With the availability of measurement of serum digitalis levels, a suspected association between digitalis and arrhythmias, at times, may be securely diagnosed, provided the serum levels and the electrocardiographic findings are correlated with other clinical findings that indicate digitalis toxicity (Fig. 2) (6).

Although in the past the incidence of digitalis toxicity was estimated to occur in 7 to 50% (average 22%) of patients taking the drug (6,13), there is no question in our mind that the incidence of cardiac toxicity has decreased rather sharply during the past 30 years. This change is due to a number of factors, including a decline in the use of digitoxin, which in retrospect was probably administered in inappropriately large doses (the usual accepted "digitalizing" dose was 1.5 mg followed by a maintenance dose of 0.1 to 0.2 mg/day). With the increased popularity of digoxin, the pendulum may have swung in the opposite direction. Although the generally accepted maintenance dose of digoxin of 0.125 to 0.25 mg, often without an initial "digitalizing" loading dose, may be appropriate for an inotropic effect, it is, as a rule, too low for the control of arrhythmias. Another important factor responsible for decreases in digitalis cardiotoxicity relates to the wide acceptance of measured digitalis serum levels. Adherence to "therapeutic levels" that often fall short of the clinically desirable end point preclude administration of toxic amounts of the drug.

Similarly, the change in the spectrum of heart disease has contributed to the decline in the incidence of digitalis toxicity. Some 25 to 35 years ago, one of the most common disorders seen in a heart clinic was rheumatic valvular disease with atrial fibrillation. Often, administration of digitalis for optimal control of the atrial fibrillation resulted in digitalis toxicity, especially in the presence of disorders that altered the response to digitalis. This is no longer the case.

**Classification of Digitalis-Induced Arrhythmias**

Although classification of the electrocardiographic manifestations of cardiotoxicity can be based on such factors as heart rate, rhythmicity and site of impulse formation, it is our belief that a classification based on probable electrophysiologic mechanisms is more rational, informative and
Figure 2. Ventricular parasystole (A) and Wenckebach type atrioventricular (AV) block (B) recorded in a patient who ingested digitoxin in an attempted suicide. The Wenckebach AV block responded promptly to atropine therapy, indicating that the digitalis effect was mediated largely through the vagus nerve. Parasystole is an unusual manifestation of digitalis toxicity. (Reproduced with permission from Fisch C, Zipes DP, Noble RJ. Digitalis toxicity: mechanism and recognition. In: Yu P, Goodwin R, eds. Progress in Cardiology. Philadelphia: Lea & Febiger, 1975.)

clinically useful. The following classification has been modified from our previous work (5,8,14):

1. Ectopic rhythms due to reentry or enhanced automaticity or both (atrial tachycardia with block, atrial fibrillation, atrial flutter, nonparoxysmal junctional tachycardia, reciprocation, ventricular premature complexes, ventricular tachycardia, ventricular flutter and fibrillation, “bidirectional” ventricular tachycardia, parasystolic ventricular tachycardia, ectopic rhythms from multiple sites of the specialized conducting tissue).


3. Depression of conduction (SA block, AV block, exit block).

4. Ectopic rhythms with simultaneous depression of conduction.

5. AV dissociation due to suppression of the dominant pacemaker with escape of a subsidiary pacemaker or due to an inappropriate acceleration of a lower pacemaker, or, rarely, dissociation with AV junctional rhythm.

6. “Triggered” automaticity (?).

Ectopic rhythms. Whereas digitalis-induced ectopic rhythms may be due to enhanced automaticity or reentry and the differential diagnosis of the two in the clinical setting is often difficult if not impossible, digitalis-induced arrhythmia probably is more commonly due to altered automaticity. There is very little doubt, for example, that nonparoxysmal

Figure 3. Nonparoxysmal junctional tachycardia. Atrioventricular (AV) dissociation is recorded in panels A to E. In panels F to H, both chambers are under control of the junctional pacemaker with the retrograde P wave located before, within and after the QRS complex. The atrial rhythms are sinus tachycardia in A and B, atrial tachycardia in C, atrial flutter in D and atrial fibrillation in E. Gradual appearance and disappearance of the nonparoxysmal junctional tachycardia is recorded in F, with varying degrees of fusion of the P waves. (Reproduced with permission from Fisch C. Tachycardias. In: Surawicz B, Reddy CP, Prystowsky EN, eds. Boston: Martinus Nijhoff, 1984:403.)
junctional tachycardia (Fig. 3 and 4), junctional escape rhythms, rare cases of digitalis-induced parasystole (Fig. 2 and 5), parasystolic ventricular tachycardia, bidirectional ventricular tachycardia (Fig. 6) and fascicular tachycardia (Fig. 7) are automatic in origin and digitalis-related. In favor of an automatic origin are the gradual appearance and disappearance of an arrhythmia (Fig. 3), the presence of fusion complexes (Fig. 5 and 7) and evidence of protection of the ectopic focus (Fig. 5). Atrial flutter, atrial fibrillation, ventricular premature complexes, ventricular tachycardia, ventricular flutter and ventricular fibrillation (Fig. 8), however, are most likely due to reentry. The latter are a less specific marker for digitalis toxicity than are the arrhythmias that are likely due to altered automaticity. Although the exact mechanism of atrial tachycardia with block is not clear, this arrhythmia may be either reentrant or automatic (Fig. 5 and 8).

Depression of pacemakers. This relatively uncommon manifestation of digitalis toxicity primarily affects the sinus node and is manifested as either sinus slowing or sinus arrest (Fig. 9). Sinus slowing may be associated with an accelerated subsidiary pacemaker (see AV dissociation). Because digitalis is rarely administered to patients with complete heart block, there is a paucity of information of the effect of toxic doses of digitalis on pacemakers other than the sinus node.

Depression of conduction. Depression of conduction due to digitalis is usually manifested as AV block or exit block (Fig. 4 and 10). The drug has minimal or no effect on myocardial conduction, either atrial or ventricular, or on the conduction of the His bundle, bundle branches or divisions of the left bundle. Consequently, intraventricular conduction disturbances are rarely induced by digitalis.
**AV block.** Although delayed AV conduction, first degree AV block and type I (Wenckebach) second degree AV block in the presence of sinus rhythm are frequent manifestations of digitalis toxicity, complete or third degree AV block is uncommon. In atrial fibrillation, however, complete AV block is a common manifestation of digitalis overdosage or intoxication. Complete AV block is less frequent when atrial flutter or atrial tachycardia is treated with digitalis. The difference is due to the greater degree of concealed AV nodal conduction during atrial fibrillation. In the presence of AV dissociation, the subsidiary pacemaker is often accelerated and this acceleration is indicative of digitalis intoxication (Fig. 3).

**Exit block.** An interesting manifestation of digitalis toxicity is exit block (Fig. 4 and 10). Exit block due to digitalis toxicity has been demonstrated in association with sinus rhythm and a variety of arrhythmias including atrial tachycardia and flutter, junctional rhythm (Fig. 4) and ventricular tachycardia (Fig. 10 and 11). The structure of the exit block may be either type I (Fig. 11B and C) or type II (Fig. 4 and 10). Regarding the mechanism of the exit block, there is convincing evidence that failure to activate the heart is due not to alteration of transmembrane action potential in the pacemaker fiber, but to failure of conduction once the impulse is initiated (15). For this reason, it is appropriate to include exit block with other forms of depressed conduction. It appears that exit block from a site other than the SA node is an exception to the case that digitalis rarely depresses myocardial conduction. In the case of the SA node, the exit block may be enhanced by the perinodal tissue that surrounds the SA node, which differs electrophysiologically from the atrial myocardium and is more sensitive to digitalis. However, there is no evidence that such transitional tissue surrounds ectopic foci.

**Ectopic rhythms and depression of conduction.** Although depression of conduction, especially AV conduction, may at times be a desired therapeutic action of digitalis, the appearance in the course of administration of digitalis of accelerated rhythms, ectopic impulses from more than one site (for example, AV junctional and ventricular rhythm) or a combination of ectopic rhythms with simultaneous depression of conduction is highly indicative of digitalis toxicity. Although the depressed conduction is usually that of the AV node, ectopic impulses may originate in one or more sites in the specialized conduction tissues (Fig. 8). Occasionally, in the presence of severe pathophysiologic...
Figure 8. Trace 1 and 2. Atrial tachycardia with high degree atrio-ventricular (AV) block, with multiformal and probably multifocal premature ventricular complexes and ventricular tachycardia. In an attempt to control the ventricular arrhythmia, pacing was instituted (trace 3). Ventricular bigeminy coupled to the paced complexes initiates a run of ventricular tachycardia (trace 4) and fibrillation. Trace 5. Administration of 50 mg bolus of lidocaine, followed by 2 mg/min infusion, suppressed the ventricular arrhythmia but without altering the atrial tachycardia. Trace 6. Atrial fibrillation with ventricular bigeminy.

Figure 9. Panel A. Wolff-Parkinson-White syndrome on the left and normal conduction on the right. Panel B. Atrial tachycardia with 1:1 conduction in lead V1 and 2:1 conduction in lead I. In lead I, the conduction is both through the bypass tract and the normal AV pathway. The 2:1 atrioventricular (AV) conduction rules out reentry as the mechanism of the atrial tachycardia. Panels C and D. AV dissociation, accelerated rhythm with right bundle branch block configuration. In middle of panel D, capture complexes with the configuration of Wolff-Parkinson-White complex are recorded. These are followed by varying fusions between the accelerated complexes with right bundle branch pattern and the QRS complex conducting through the bypass tract. The differential diagnosis between ventricular tachycardia and junctional rhythm with aberration is impossible, because in the presence of a bypass tract, both could fuse with atrial impulses. In panel E (lead II), atrial tachycardia with 2:1 AV conduction is followed by sinoatrial suppression and junctional escape rhythm. The same phenomenon is recorded in lead V2 (Reproduced from Fisch C, Pinsky S. Wolff-Parkinson-White syndrome. Circulation 1957;16:1004, with permission of the American Heart Association, Inc.)

Figure 10. Trace 1. Atrial fibrillation with junctional escape complexes (for example, complexes 5, 8, 9) at an RR interval of 1.0 second. Trace 2. Ventricular bigeminy. Trace 3. Ventricular tachycardia with 3:2 Mobitz type II exit block. The longer than established interjunctional interval of 1.0 second that follows complexes in trace 2 indicates concealed retrograde conduction of the premature ventricular complexes with suppression of the junctional pacemaker. (Reproduced with permission from Fisch C, Knoebel SB. Recognition and therapy of digitalis toxicity. Prog Cardiovasc Dis 1970;13:71.)
Figure 11. Panels A, B, C and D, recorded from four different patients, illustrate ventricular tachycardia after supraventricular tachycardia. The dominant cycle length of the supraventricular tachycardia and the ventricular "escape" cycle are indicated in milliseconds. In panels B and C, ventricular tachycardia is associated with 3:2 Wenckebach exit block. This figure illustrates what might represent clinical examples of "triggered" automaticity. (Reproduced with permission from Fisch C, Knoebel SB. Accelerated junctional escape: a clinical manifestation of triggered automaticity. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology and Arrhythmias. Orlando: Grune and Stratton [in press].)

Figure 12. Double junctional rhythm with RR and PP intervals of approximately 0.96 and 1.08 seconds, respectively.

Figure 13. Accelerated junctional escape after an accelerated premature complex. The upper and lower traces were recorded in two different patients. Such arrhythmias may be a clinical expression of "triggered" automaticity in human beings. (Reproduced from Knoebel SB, Fisch C. Accelerated junctional escape. Circulation 1974;50:151, with permission of the American Heart Association, Inc.)

Figure 14. The three traces are sections of a continuous record and illustrate sinus rhythm interrupted by ventricular tachycardia followed by a junctional tachycardia. The bottom trace shows fusion P waves and reemergence of a dominant sinus P wave. This record may be an example of "triggered" automaticity with the junctional tachycardia triggered by the ventricular tachycardia.
alterations, the ectopic rhythm may originate in the myocardium.

**AV dissociation.** AV dissociation may result from slowing of the dominant pacemaker and the assumption by a subsidiary focus, usually junctional rhythm, of pacemaker function. On the other hand, the dominant pacemaker rate may remain normal, but its function usurped by an accelerated subsidiary pacemaker, again most often junctional rhythm (Fig. 3). An interesting and a relatively rare manifestation of digitalis-induced AV dissociation is a double junctional rhythm due to intranodal dissociation with the atria and ventricles activated by two separate AV nodal pacemakers (Fig. 12).

**Triggered automaticity.** Although “triggered” automaticity is a form of automatic rhythm, its behavior is different from the conventional automatic rhythms. Because “triggered” automaticity may prove to be another mechanism responsible for digitalis-induced automaticity, the arrhythmia is currently of considerable interest. The cellular basis for and the behavior of “triggered” automaticity are described elsewhere in this symposium. It has been suggested that some disorders of rhythm in animals (16,17) and human beings (18,19) may reflect the “triggered” automaticity recorded in an isolated cell.

The clinical manifestations suggestive of “triggered” automaticity include: 1) accelerated junctional impulses after premature ectopic impulses, the latter acting as the “triggering mechanism” (Fig. 12); 2) less common, ventricular arrhythmias “triggered” by supraventricular tachycardia (Fig. 13); and 3) even more rare, junctional tachycardia “triggered” by ventricular tachycardia (Fig. 14). Although these arrhythmias are often observed during digitalis administration and behave in a manner similar to that of the “triggered” arrhythmias observed in the isolated cell exposed to toxic doses of digitalis, extrapolation from a cellular mechanism to a clinical arrhythmia must be performed with caution. Further studies of clinical arrhythmias suspected to be “triggered” in origin are needed before the mechanisms observed at the cellular level can be assumed to be responsible for arrhythmias in the intact heart.

**Conclusions**

Digitalis toxicity was described by Withering (1) in 1785. His understanding and comprehensive descriptions of the actions and the effects of the drug, arrived at by sheer power of observation and without the aid of a single graphic tool, have stood the test of time. In the 200 years that followed, our knowledge of the glycoside and its effect on the heart has been considerably refined, but the proper use of digitalis must still be clinically determined. Notwithstanding the impact of the electrocardiogram, sensitive methods for measuring plasma levels of the glycosides and information gained through cellular electrophysiologic studies, assessment of the adequacy of digitalization or digitalis-induced arrhythmias continue to be an art. This report presents our suggestions that an approach to electrocardiographic manifestations of arrhythmias based on electrophysiologic mechanisms may eventually allow more precise determination of adequacy of digitalization for control of arrhythmias, as well as recognition of digitalis-induced arrhythmias.

**References**