Digitalis Intoxication in Patients with Atrial Fibrillation

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SUMMARY

The characteristic arrhythmias induced by digitalis glycosides in patients with atrial fibrillation are illustrated, and their mechanisms are described. The two effects of the drug which are most important in the genesis of such disturbances are: production of A-V nodal block and arousal of subsidiary pacemakers. These properties account for slow ventricular responses, escape beats, and nonparoxysmal junctional tachycardia. Less commonly observed arrhythmias include exit block from junctional pacemakers, and bidirectional tachycardia which may reflect blocking actions of digitalis in subnodal tissues. The recent development of His bundle electrocardiography and the immunoassay method of blood level determination permit more accurate appraisal of the clinical status of patients in whom digitotoxicity is suspected. Treatment of junctional rhythms due to digitalis intoxication is usually passive. The occasional use of drugs, pacing, or cardioversion is discussed.

Additional Indexing Words:
Nonparoxysmal junctional tachycardia   Exit block   Entrance block   Escape beats
Bidirectional tachycardia   His bundle electrocardiography

Some of the most dramatic therapeutic successes produced by digitalis occur in patients with congestive failure and atrial fibrillation. Its use in this clinical setting is well established, but the presence of digitalis intoxication under such circumstances is frequently overlooked.

To recognize the presence of digitalis intoxication in patients with atrial fibrillation, one must pay particular attention to the electrophysiologic events which occur in the atroventricular junction. It is our purpose here to discuss the characteristic arrhythmias which develop in this condition and to review the developments which have been reported in the last 5 years.

Disturbances of Rhythm
Digitalis and A-V Nodal Conduction

The digitalis effect of greatest electrophysiologic importance in patients with atrial fibrillation is the characteristic prolongation of A-V nodal refractoriness. The slowing in ventricular response to atrial fibrillation, thereby induced, constitutes the drug's principal application in such cases. With the availability of His bundle electrograms, the site of digitalis-induced block has been clearly localized in man to tissues above the point where the His bundle spike is recorded, and this is surely the A-V node.3, 4

The number of impulses recorded from within the atrium during atrial fibrillation is greater than the A-V node can transmit. Many of these signals will actually enter the A-V node, but the degree of penetration will vary as a function of their rate and the conducting characteristics of the patient's A-V node.5 Partial penetration by atrial fibrillation impulses into the A-V node will prolong its refractoriness, thus making more difficult the penetration of subsequent impulses. It follows, therefore, that the more rapid the atrial rate, the more partial penetration will occur and the slower the ventricular response. The heart rate decreases when a patient's rhythm changes spontaneously from atrial flutter to atrial fibrillation or when induced atrial fibrillation is compared with paced atrial tachycardia.6-8 The number of atrial signals which reach the A-V node in atrial fibrillation is variable. It seems logical that with more rapid atrial fibrillation the ventricular response would be slower, all other features of A-V nodal refractoriness being equal. If digitalis does in fact increase the atrial fibrillatory rate, then more concealed conduction would be expected, and the ventricular rate would accordingly decrease.

Analysis of A-V nodal conduction in atrial fibrillation is further complicated by the variable inherent refractoriness of different A-V nodes.9

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They are affected by the outflow from the autonomic system and by other poorly defined pathologic processes which increase refractoriness. Thus different amounts of digitalis will be required to achieve satisfactory ventricular rate control among different patients. In confirmation, Chamberlain et al. found a poor correlation between resting ventricular rate during atrial fibrillation and digoxin blood levels.\textsuperscript{10}

**Escape Beats**

A slow ventricular rate in patients with atrial fibrillation is an important indication of possible digitalis toxicity. Such bradycardias develop because fewer atrial impulses are transmitted through the A-V node as its refractoriness is progressively increased. If the node were so affected that total blockage occurred, the ventricles would stop beating. They do not, of course, because escape pacemakers located in the A-V junction discharge to protect the heart from asystole. The escape foci most likely to function under such circumstances are thought to be located within the A-V junction, more specifically in the N-H region of the A-V node or in the bundle of His. Such automatic cardiac tissue has the intrinsic property of diastolic depolarization whereby cells will reach threshold potentials and discharge unless suppressed by more rapid impulses such as those ordinarily transmitted through the A-V node from the atrium.

The escape rate of junctional pacemakers in adult man is probably between 45 and 55 beats/min. If an impulse does not pass through the A-V node in an interval corresponding to the automatic cycle of the particular pacemaker cells, then an escape will appear. The appearance of this first escape beat signifies an instant of atrioventricular dissociation although we do not conventionally assign this diagnosis. The more escape beats appear, the more complete is the electrophysiologic dissociation between atria and ventricles.

Escape beats terminate the longest asystolic intervals on the electrocardiogram and can be identified by this characteristic property. When escapes dominate, the R-R intervals will be almost equal. Usually the first of a series of escape beats follows an even longer interval because the focus has been suppressed below its intrinsic escape rate by transmitted impulses. If escaping continues, the focus “warms up” and discharges slightly faster.

The location of these escape foci is important. As a general rule, the nearer to the A-V node the intrinsic pacemaker, the more rapid its spontaneous rate of discharge. With the A-V node as the site of digitalis-induced A-V block, the escape foci are located relatively high in the ventricular specialized conduction system. The supraventricular appearance of most escape foci suggest their origin above the bifurcation of the bundle branches. His bundle records of such escape foci show the same general characteristics as for sinus beats except, of course, for the absence of associated P waves.\textsuperscript{11}

Sometimes escape beats seen in patients with digitalis overdose have a slightly aberrant form, usually of incomplete right bundle-branch block configuration (fig.1). This finding has been ascribed to their A-V junctional origin with conduction to the ventricles over such unusual pathways as the Mahaim fibers.\textsuperscript{12} Alternatively, junctional impulses may find some portions of the Purkinje system unable to conduct normally at slow rates because of partial depolarization.\textsuperscript{13, 14} Recent evidence suggests that such beats may originate slightly “downstream” from the His bundle, possibly in the proximal fascicles of the left bundle branch.\textsuperscript{15, 16}

The shorter-than-normal H-V intervals found in

![Figure 1](image_url)

**Figure 1**

Atrioventricular junctional escapes with aberrancy in the presence of atrial fibrillation. Electrocardiogram lead aV_{1}. Frequent impulses from the fibrillating atria enter the atrioventricular junction but are prevented from penetrating to the ventricles by the high degree of entrance block produced by digitalis. The escape pacemaker then discharges at an interval of 1.32-1.36 sec (rate of 44 beats/min) and is conducted in an aberrant fashion to the ventricles (X). The entrance block, however, is not sufficient to block all atrial impulses. A few are transmitted (QRS) with normal intraventricular conduction. Note that the escape intervals are the longest on the record. Recent studies suggest that such aberrant escapes may originate in the proximal fascicles of the bundle branches.\textsuperscript{15} (Reprinted from Ann Intern Med, by permission.)
such cases may be due to retrograde depolarization of the His bundle from these "sub-His" pacemakers. Why "higher" junctional foci do not preferentially discharge in these cases is not known. Either they are suppressed or the lower pacemakers have been accelerated above the rate of the junctional foci. Most escape beats with supraventricular QRS may take origin in the His bundle itself since much of the A-V node, at least in animal models, appears to be without pacemaker potential.\textsuperscript{17,18} However, in man the exact location of supraventricular escape pacemakers has not been established, and we would prefer to continue to use the somewhat general term "A-V junction" unless this issue has been more precisely resolved.

In addition to producing block, digitalis also stimulates ectopic pacemakers to discharge rapidly. Familiar clinical examples of this property are the development of ventricular beats, idioventricular rhythms including ventricular tachycardia, and ectopic atrial tachycardia. Apparently digitalis exerts relatively early stimulating effects upon A-V junctional pacemakers because in patients with atrial fibrillation accelerated junctional rhythms are commonly seen before ventricular irritability is evident.\textsuperscript{19}

**Nonparoxysmal A-V Junctional Tachycardia**

While it is slowing ventricular response by increasing A-V block, digitalis may "paradoxically" raise the heart rate by accelerating the escape focus. The clinical result is the production of a regular pulse often in the "normal" range of 70-100 beats/min (fig. 2). This may lead one to conclude that normal sinus rhythm has been reestablished. However, the development of a regular rhythm in any patient with chronic atrial fibrillation should suggest the possibility of digitalis intoxication. Patients with paroxysmal atrial fibrillation may often be successfully converted to sinus rhythm when digitalis is administered, but this seldom happens when the drug has been given for rate control in a patient with long-standing atrial fibrillation. Much more likely the regularization will result from the development of nonparoxysmal A-V nodal (junctional) tachycardia, as this characteristic digitalis-toxic arrhythmia has been termed by Pick.\textsuperscript{20} Since the rate is faster than the "normal" escape rate of the subsidiary pacemaker, the word tachycardia may reasonably be applied. This arrhythmia has been increasingly recognized as a common manifestation of digitalis intoxication.\textsuperscript{19} It is certainly more common than the well-known arrhythmia atrial tachycardia with block.

Although digitalis is the usual cause of these accelerated junctional rhythms, they also occur with
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acute inferior myocardial infarctions, with myocarditis (especially that due to rheumatic fever), and after intracardiac surgical procedures. Under these circumstances sinus rhythm is frequently present, and the A-V dissociation is more easily recognized. However, in the presence of atrial fibrillation, the only clue may be the regularization of the ventricular response.

The resolution of nonparoxysmal A-V junctional tachycardia after digitalis is discontinued may follow several courses. This will be determined by the relative speed with which the A-V block and the accelerated pacemaker are released from the toxic effects of digitalis. If block resolves quickly and the accelerated pacemaker slows more gradually, then the ventricular response will become irregular but the R-R intervals will seldom be longer than the discharge interval of the still-accelerated subsidiary pacemaker. If the opposite occurs and A-V block continues while the junctional pacemaker rate decreases, then regularization will persist as the heart rate slows. Thus in patients with atrial fibrillation who may be toxic from digitalis, A-V block decreases and regularizes the rate while pacemaker stimulation increases the rate.

Clinicians frequently encounter tracings which show a "tendency toward regularization;" that is, repetitive R-R intervals are seen occurring at various points throughout the record. Such incomplete regularization is easily and probably frequently overlooked during routine electrocardiographic analysis. The studies of Urbach and his colleagues with computerized R-R histograms clearly remind us of this frequent oversight.21,22 When partial regularization is seen, the patient should be questioned for symptoms of toxicity, and a digitalis blood level should be obtained.

When digitalis intoxication complicates cor pulmonale, paroxysmal atrial tachycardia with block is more likely to be produced than accelerated junctional rhythms which are rather uncommon in this setting. These observations raise the interesting possibility that diseases predominantly affecting the right atrium like cor pulmonale tend to be associated with such relatively organized arrhythmias as ectopic atrial tachycardia, multifocal atrial tachycardia, and atrial flutter.23,24 Atrial fibrillation is found more commonly when the left atrium is primarily affected as in mitral valve disease or coronary artery disease.

Nonparoxysmal Junctional Tachycardia
vs Paroxysmal Supraventricular Tachycardia

Occasionally digitalis may accelerate a junctional rhythm to rates which approach those associated with such conditions as paroxysmal atrial and nodal tachycardia. The mechanisms and characteristics are sufficiently different to warrant careful distinction. Paroxysmal supraventricular (atrial or nodal) tachycardia (SVT) is a relatively common process often found in young patients with apparently normal hearts. It begins and ends suddenly in contrast to the nonparoxysmal digitalis-induced junctional rhythms which more gradually appear and disappear. SVT develops in the setting of sinus rhythm, but P waves may be difficult to discern from the external electrocardiogram during the tachycardia, and one could conclude that the atria might be fibrillating.

Our understanding of the character of supraventricular tachycardia has been significantly clarified in recent years by the work of Goldreyer, Bigger, Damato, and others.25-27 In the overwhelming majority of cases, the arrhythmia appears as a series of atrial echoes usually, but not always, induced by a premature atrial beat. The A-V node itself is an integral part of the pathway which perpetuates this reentrant arrhythmia. A few atrial tachycardias are ectopic in origin and not perpetuated by A-V nodal reentry. In all likelihood, the variety produced with digitalis intoxication is of this type and, like atrial flutter, can be partially blocked in the A-V node.28 (This topic is developed more fully in other sections of this symposium.)

Despite these considerations, the diagnosis between digitalis-induced nonparoxysmal junctional tachycardia and paroxysmal supraventricular tachycardia may be quite difficult to make in a few cases. For example, let the physician be faced with a regular tachycardia at, say, 150 beats/min with supraventricular-type QRS and no obvious atrial activity in a sick patient whose digitalis status is unknown. Vagal-stimulating maneuvers have not affected the arrhythmia. In such circumstances, the blood digoxin or digitoxin concentration obtained by the immunoassay method may be of great diagnostic importance.29,30 While this test is being performed, and if the patient's general condition permits, an intraatrial electrogram should be obtained either at the bedside or under fluoroscopic guidance. The presence of atrial fibrillation can thus be established. Treatment will follow based on the results of these investigations.

Circulation, Volume XLVII, April 1973
Entrance and Exit Blocks

We have seen how a rapid regular rhythm, in the presence of atrial fibrillation, may be due to digitalis intoxication. However, occasionally one may encounter a rapid irregular rhythm produced by the drug, much like the finding in a patient with atrial fibrillation who has not received digitalis. If additional digitalis were given to such a patient, even more dangerous arrhythmias could follow.

What is the mechanism of digitalis-induced rapid irregular ventricular rhythm with supraventricular configuration? The current explanation is that the ventricles are driven by an accelerated junctional pacemaker with intermittent block below that site. The phenomenon is termed exit block in contrast to entrance block into the A-V node above the junctional pacemaker. The term entrance block is used in referring to the characteristic feature of A-V nodal tissue, its ability to delay conduction. Impulses entering the node encounter increased refractoriness and are blocked in varying degrees as they traverse the node. Exit block implies a partial or complete obstacle to impulses which leave the region of a pacemaker and try to stimulate surrounding cardiac time. Sinoatrial exit block is a familiar example.

Nonparoxysmal Junctional Tachycardia with Exit Block

The published examples of this arrhythmia have been identified by the presence of Wenckebach periodicity and its characteristic shortening R-R intervals separated by pauses (fig. 3).

![Diagram of lead V1 showing atrial fibrillation and resultant ventricular rhythm with exit block](image_url)

Figure 3

Nonparoxysmal junctional tachycardia with Wenckebach type of exit block. The strip of lead V1 shows atrial fibrillation and apparently the usual irregular ventricular response. However, closer scrutiny discloses characteristic periods of shortening R-R intervals separated by pauses. Although not shown, a pause precedes the first complex, and hence the first three beats, and the pause that follows them constitutes one Wenckebach period. The inherent rate of the functional pacemaker can be determined by dividing this time interval (2.72 sec) by 4 (three manifest beats plus the blocked one), giving 0.68 sec, corresponding to a rate of 88 beats/min. The sequence is repeated in the second period shown. The mechanism involved is diagrammed beneath the lead, using an assumed inherent delay in transmission of the junctional impulse of 0.26 sec and further increments of delay of 0.22 and 0.08 sec. Note that R-R intervals shorten because successive increments of block are shorter. The pause equals two pacemaker cycles less the sum of the increments (0.22 + 0.08 = 0.30 sec). Broken lines indicate block of retrograde transmission of the junctional impulse. Thus, analysis of the tracing indicates that an accelerated atrioventricular junctional rhythm is present (at a rate of 88 beats/min), with both entrance block of atrial impulses from above and Wenckebach exit block of the junctional impulses into the ventricles. Numbers in hundredths of a second. (Reprinted from Ann Intern Med, by permission.)
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elsewhere in this symposium for a discussion of the different types of A-V block.) A rapid and irregular ventricular response in a presumably well-digitalized patient should raise the question of junctional tachycardia with Wenckebach type of exit block. One must seek the repeated pattern of shortening R-R intervals separated by pauses as evidence of this.

An important reservation must now be made about this unusual arrhythmia. To my knowledge, no record with His bundle electrograms has been published of a digitalis-induced nonparoxysmal junctional tachycardia with exit block. Such data would be very helpful because the locus of the pacemaker in such cases has not been definitely established although it is assumed to be in or near the His bundle. Wenckebach block in such cases must occur below the pacemaker whereas in most cases the Wenckebach phenomenon is produced in the A-V node itself, above the subsidiary pacemaker.31 However, Wenckebach periodicity has been found in the ventricular specialized conduction tissues below the A-V node and presumably such is the case with this arrhythmia.33-35

Bidirectional Tachycardia

When digitalis intoxication goes unrecognized at the stage of accelerated junctional rhythms, with or without exit block, the next and frequently final arrhythmia may be bidirectional tachycardia (fig. 4).36-38 This extremely serious abnormality has recently been suggested to reflect the toxic effects of digitalis on conduction in the peripheral ventricular conducting system. The accelerated pacemaker in such cases is assumed to be in the A-V junction.

Right bundle-branch block is often, though not always, present, and conduction in the left ventricle has been postulated to occur alternately over the anterior and posterior divisions of the left bundle. Rosenbaum, Elizari, and Lazzari found this combination in the 12-lead electrocardiograms of 13 patients with bidirectional tachycardia.39 Not all bidirectional tachycardias may have this mechanism, however. We have recently studied a patient with this arrhythmia not due to digitalis toxicity. All beats had right bundle-branch block appearance. Left- and right-axis deviation alternated in the frontal-plane leads. His bundle records showed that both types of beats originated in the ventricles, not the A-V junction (Kastor JA, Goldreyer BN: Unpublished observations).

Many observers in clinical electrocardiography have commented that digitalis does not produce intraventricular conduction blocks. This experience, however, is at variance with the animal experimental data.40, 41 It may be that, with advanced toxicity in severely diseased human hearts, slowing of conduction in the bundle branches can occur. Partial peripheral block is the setting for actual dropped beats in Mobitz type II block. Careful studies with intracardiac records may reveal some instances of this conduction disturbance caused by digitalis toxicity.

Sequential Development of Toxic Arrhythmias in the A-V Junction

At this point it should be emphasized that throughout all phases of progressive intoxication there may be no ventricular premature beats to provide a more familiar clue to the presence of overdosage. The entire process may develop because of A-V nodal entrance block, acceleration of junctional pacemakers, exit block out of such pacemakers, and variable intraventricular block. Furthermore, the progression need not occur in a regular pattern. One may be faced at the outset with a rapid irregular rhythm, seemingly unresponsive to digitalis. Although such factors as pulmonary embolism, hypoxia, hypovolemia, anemia, hyperthyroidism, and fever must be considered as partly responsible for the rapid rate, one must bear in mind that not more, but less digitalis may be required.

Aberrancy vs Ectopy

The production of ventricular premature beats is a common toxic effect of digitalis. The differentiation of such beats from aberrantly conducted
supraventricular beats must frequently be made in patients with atrial fibrillation. Recognition is essential, for aberrancy is often a physiologic phenomenon whereas ventricular irritability may reflect digitalis intoxication.

Aberrant conduction from atria to ventricles occurs when part of the intraventricular conduction system is partially or wholly refractory to the beat being conducted out of the A-V node. The right bundle branch is more likely to be affected and, as a result, most aberrantly conducted beats have right bundle-branch block configuration. This is not exclusively the case, however, since hemiblocks and left bundle-branch blocks may also occur.

Intermittent aberrancy develops most commonly when a beat is conducted with a short coupling interval after a long previous cycle. This phenomenon, when it occurs in atrial fibrillation, is known as the Ashman phenomenon. Since most aberrantly conducted beats have right bundle-branch block, certain morphologic characteristics are frequently found in lead V1: (1) identical initial vector to the normally conducted beat; (2) triphasic contour (rsR'). Ventricular premature beats tend to be followed by a "pseudocompensatory" afterpause while aberrant beats need not. The arrangement of aberrant beats in groups of two or more is not uncommon, whereas ventricular ectopic beats are more likely to appear in bigeminy. Bigeminal beats are also frequently coupled by constant intervals to the previous beat, which is not necessarily the case in aberrancy. To confuse the matter, ventricular parasystole is not fixed coupled, but this arrhythmia is almost never due to digitalis intoxication. The Ashman rule, moreover, is not always helpful, since ventricular premature beats also appear after long previous cycles (the rule of bigeminy).

Although these several clues can be applied in many cases, often it will not be possible, by standard electrocardiographic means, to make the correct diagnosis. Reliance must then be placed on correlative clinical data and blood glycoside determinations. If the proper facilities are available, intracardiac records can be made which will usually settle the issue.

**Treatment**

Most episodes of digitalis intoxication are incorrectly treated because they are not properly recognized, and more of the drug is administered. Thus, identification of the problem is the first and most vital step.

Treatment of digitalis toxicity is usually simpler than the long dissertations on the subject would suggest since in most cases, and particularly in patients with atrial fibrillation, the best course is studied, monitored nontreatment. Stop the digitalis, correct electrolyte abnormalities, and observe the patient carefully. Many of the pharmacologic agents recommended for treatment of digitalis intoxication have significant side effects of their own.

Specific treatment may be required, however, when hemodynamic compensation is jeopardized or fails because of an inordinately slow or rapid heart rate, and if ectopic activity threatens to deteriorate into a potentially fatal ventricular arrhythmia. When the ventricular rate has decreased excessively, cautious use of isoproterenol or a temporary percutaneous intracardiac pacemaker may be indicated. Particular care should be taken with the catecholamine drugs which may arouse ventricular irritability in digitoxic patients. Atropine may be given but is unlikely to release the A-V block in most cases. The presence of slow rates implies that the A-V nodal blocking effect of digitalis dominates in such patients without significant acceleration of lower centers. High-grade exit block out of a subsidiary pacemaker could account for severe bradycardia but is probably quite rare.

To suppress ventricular ectopic beats when they are caused by digitalis toxicity, the various antiarrhythmic drugs including lidocaine, diphenylhydantoin, procainamide, quinidine, or propranolol may be given. Potassium is also frequently helpful. Occasionally rapid overdrive pacing may find use in temporally suppressing dangerous ventricular irritability in patients with digitalis intoxication. It is interesting to note that despite the effectiveness of this technic, the rate of hidden ectopic impulse formation may actually be increased.

Relatively few reports are available regarding the use of drugs in the treatment of junctional tachycardias when induced by digitalis. The probable reason is that these arrhythmias are usually managed without specific intervention. The rates are not often rapid, and the danger of a more lethal arrhythmia developing is slight unless evidence of ventricular irritability is present. Furthermore, many of the drugs conventionally selected for use in digitoxicity may increase atrioventricular block, the presence of which is almost always a feature of accelerated junctional rhythms in this setting. Cardioversion should not be employed for treatment of digitalis-induced nonparoxysmal junctional tachycardia.

_Circulation, Volume XLVII, April 1973_
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The perfect antidote to reverse digitalis toxicity is not yet available. However, a very promising immunologic method is being developed. The same approach which has already proven so valuable in determining the blood level of the drug may soon provide us with a tool which can leach the glycosides from the myocardium.\textsuperscript{51, 52} Results in animals are very promising, and purification of the antibody will hopefully allow its use in patients with digitalis intoxication.

Acknowledgments

The author would like to thank, in particular, Dr. Peter M. Yurchak, Massachusetts General Hospital, Boston, Massachusetts, who collaborated in previous work on this subject. The continued support and helpful advice of Dr. Alfred P. Fishman, Director Cardiovascular-Pulmonary Division, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, is also much appreciated. The manuscript was typed by Miss Ellen Strauss and Mrs. Marion Brooks.

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Circulation. 1973;47:888-896
doi: 10.1161/01.CIR.47.4.888

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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