CLINICAL PROGRESS

Digitalis and the Electrocardiogram

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The action of digitalis and related glycosides is reflected in the electrocardiogram in a manifold fashion. Apart from altering the speed and mode of ventricular repolarization, represented by the ST-T portion, practically any type of disturbance in the formation or propagation of the cardiac impulse can result from digitalis medication; on the other hand some of these disorders of rhythm occurring spontaneously, may disappear on exhibition of the drug. Whether a therapeutic or a toxic effect will prevail, and the time until one or the other becomes manifest, depend on a number of variables and cannot be predicted in a given case. Whereas the dose and mode of administration can be adjusted according to estimated needs, other factors that may largely influence the outcome of therapy are more difficult to assess in a clinical evaluation of the individual patient. This difficulty refers to the complexity of electrolytic disorders associated with congestive heart failure, the condition of the myocardium, and the speed and extent to which the glycoside is absorbed, metabolized, and excreted. It is for this reason that each new digitalization, and determination of a maintenance dose, should be viewed as a therapeutic experiment at the bedside, the outcome of which is uncertain. The decision to continue or to interrupt medication, and in what manner to change the basic therapeutic plan, will depend largely on the electrocardiographic control of the early therapeutic results.

In table 1 the most common electrocardiographic manifestations of digitalis action are arranged from the viewpoint of their practical clinical significance, regardless of the various underlying physiologic mechanisms. Thus in the first column are listed “therapeutic” effects, that is those alterations that may be considered as “safe” with regard to continuation of digitalization according to plan. These include deformation of the ST segment to a sagging appearance, lowering of the T wave, obvious or apparent shortening of the Q-T duration, and moderate depression of A-V conductivity causing prolongation of the P-R interval within the range of 0.20 to 0.30 second during sinus rhythm, and slowing of the ventricular rate—one of the spectacular effects of digitalis therapy—in rapid atrial arrhythmias (paroxysmal tachycardia, flutter, and fibrillation). Reduction of the ventricular rate under the latter circumstances may become so pronounced that a subsidiary pacemaker, usually one originating in the A-V node, may escape for 1 beat or for several successive ones. Intermittent A-V dissociation induced in this manner in atrial fibrillation should not preclude further digitalization, provided that the average ventricular rate is not less than 50 nor more than 70. Beyond these limits onset of persistent A-V dissociation (with very slow or very fast regular ventricular rates) can be expected, which requires a reduction of the digitalis dose applied.

Apart from reducing the ventricular rate in rapid ectopic atrial rhythms in this manner, digitalis may affect the abnormal atrial mechanism itself. When the response of cases with atrial tachycardia, flutter, or fibrillation is closely followed in the electrocardiogram, 2 seemingly contradictory effects can be observed. Usually the rapidity of the atrial deflections is enhanced, and the slower types (tachycardias and flutter) are converted, sooner or later, to the most rapid one—fibrillation. Often, however, particularly when digitalization is started soon after the onset of paroxysmal rapid heart action, atrial action slows, the abnormal mechanism is stopped, and sinus rhythm is restored. The background for this apparent paradoxical

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behavior of the atria on different occasions is the known double action of digitalis upon the atrial myocardium. By its direct action it tends to depress conductivity and to slow propagation of the rapid impulses; by its simultaneous indirect action, via the vagi, it tends to shorten the refractory phase of the atrial myocardium and thus to enhance its conductivity. Depending on the dominance of one or the other of these 2 effects, rapid atrial activity will either be stopped, or be maintained and augmented. This is one of the clinical situations when unpredictability of digitalis effects is exemplified clearly in the electrocardiogram. But, regardless of the outcome of such an experiment, the patient will benefit from it because the ventricular rate slows due either to restoration of sinus rhythm or depression of A-V conductivity accompanying acceleration of the atrial action.

In the second column of table 1, under the heading "excessive," are listed disorders of impulse conduction or formation, as well as their combinations, all of which, when induced by digitalis, require great caution in continuation of the medication because they may herald severe and dangerous stages of digitalis toxicity. With one exception, initiation of atrial fibrillation from pre-existent sinus rhythm, a rather rare event, they usually require an electrocardiogram to establish a proper diagnosis. This is pertinent, since some of these disorders have specific clinical significance. Thus it has been recognized recently\(^1\) that an ectopic atrial tachycardia with irregular ventricular response may develop following doses of digitalis ordinarily considered as therapeutic when the drug is employed in potassium-depleted states, e.g., subsequent to a massive diuresis. Less well known, but common in our own experience, is a complete A-V dissociation engendered not by A-V block, but by acceleration of the ordinarily subsidiary A-V nodal pacemaker (to rates between 70 and 100). When this occurs in the presence of atrial fibrillation, the regularization of the ventricular rhythm may be mistaken at the bedside for conversion to sinus rhythm.

Slowing of a sinus tachycardia by digitalis should be attributed to abatement of heart failure rather than to a direct action of the drug upon the primary pacemaker. When, during sinus rhythm, the ventricular rate drops below 50, development of an advanced conduction disturbance, usually involving the A-V junctional tissues, must be suspected and verified in the electrocardiogram. Irregular A-V conduction in sinus rhythm (second degree A-V block type I, i.e., with Wenckebach periods), and its progression to complete A-V dissociation with a slow ventricular rate, must be viewed as signs of digitalis excess. This block remains the main evidence of digitalis toxicity when the myocardium is unaffected by disease, e.g., when large amounts of digitalis are consumed accidentally by children, or in suicidal attempts by adults. When second degree A-V block develops after therapeutic doses in young persons with febrile conditions, the presence of an acute myocarditis is strongly suggested.

Among other types of conduction disturb-
ances, only S-A block is attributable to digitalis action; in fact, digitalis is its most common cause. Intraventricular block, on the other hand, is not a typical consequence of digitalis medication. On the contrary, its disappearance is frequently observed in the course of effective digitalization. S-A block with its long ventricular pauses leads to escape of subsidiary centers and thus to the establishment of slow nodal rhythms with A-V dissociation or with persistent retrograde conduction of the impulse to the atria. The latter may be associated with depression of A-V conductivity, likewise induced by digitalis, and then conditions are favorable for the development of reciprocal beating of the ventricles.

While all these disorders of rhythm must be considered to represent states close to digitalis toxicity, the need to discontinue the medication at once, under all circumstances, is not as strict as in the case of ectopic impulse formation in the ventricles. When heart failure is not severe, or partially controlled by the digitalis dose that produced the arrhythmia, it is best to interrupt the medication for a few days and to resume it with a reduced dose. When the condition of the patient is critical and the demand for therapy is acute, continuation of treatment is feasible as long as more severe signs of toxicity, (ventricular ectopic beats) do not show up in frequent electrocardiographic controls. It would appear that the combined administration of potassium and digitalis may be of value in keeping the patient at such "sub-toxic" levels if there is great urgency for digitalis maintenance.

Listing of premature systoles and paroxysmal tachycardia of ventricular origin in the last column of table 1, under the heading of digitalis toxicity, does not imply that every patient revealing this type of arrhythmia should automatically be excluded from the benefits of digitalis therapy. Ventricular ectopic impulse formation may be a manifestation of myocardial pathology or of a failing heart and may disappear upon digitalis medication. However, when such ectopic beats develop soon after initiation of digitalis therapy or in the course of protracted medication, danger may be imminent and the medication must be stopped. If, as is sometimes the case, information concerning preceding digitalization is unobtainable, the following electrocardiographic features are helpful in establishing the diagnosis of digitalis toxicity: (1) fixed coupling of premature beats of variable bizarre contour, resulting in ventricular bigeminy; (2) their multiplication in short runs; (3) a so-called bidirectional type of paroxysmal tachycardia, and (4), of course, other electrocardiographic changes attributable to digitalis action, such as the typical ST-T deformation and the various degrees of A-V block mentioned previously.

Premature ventricular systoles and ventricular tachycardia may be erroneously diagnosed when aberrant ventricular conduction has developed as a consequence of a rapid ventricular rate, e.g., in paroxysmal atrial fibrillation. The differential diagnosis is of great practical importance since, in the latter case, intensification, and, in the former, interruption of digitalis medication is indicated. Admittedly, however, situations may arise where the diagnosis or exclusion of digitalis toxicity remains a matter of trial and error.

Ventricular fibrillation, the most advanced stage of digitalis intoxication is, fortunately, a rare event although it is known to occur precipitously on occasion in individuals particularly sensitive to the drug. In most cases it can be avoided by recognition of the premonitory signs noted above and their proper handling in time.

Bigeminy and associated signs of digitalis excess will disappear spontaneously once the medication has been stopped, but this may take some time, even weeks, during which the clinical condition may necessitate active treatment. Attacking digitalis-induced ectopic ventricular beats by quinidine or procaine amide is hazardous since, paradoxically, these 2 drugs may enhance rather than abolish the ectopic impulse formation under such circumstances (probably by creating conditions favorable for multiplication of a ventricular reentry mechanism). If the need for immediate control of the abnormal mechanism is great, intravenous injection of 20 ml. of magnesium sulfate (20 per cent) may transiently suppress the ectopic beats even in most advanced forms of toxicity. Impressive and long lasting effects
may be achieved by oral administration of potassium chloride, 2 to 3 Gm. every 3 to 4 hours. This agent too, however, has its pitfalls. It cannot be used when renal failure accompanies heart failure and, in our experience, it may counteract not only digitalis toxicity but also the therapeutic effects of the drug.

On an empirical clinical basis it would appear that some balance is necessary between digitalis and potassium concentrations in the organism in order to achieve an optimal therapeutic effect. A disturbance of this equilibrium in one or the other direction will lead to clinical and electrocardiographic signs of digitalis poisoning, or to failure of digitalis to act therapeutically. The optimal value of this "digitalis/potassium ratio" is unknown and perhaps varies from case to case. While at present, therefore, the simultaneous use of digitalis and potassium salts rests on uncertain empirical grounds, an approach to the solution of this vital clinical problem has been provided by recent investigations concerning the action of drugs and electrolytes upon the single myocardial cell.

Methods have been developed in several physiologic laboratories for introduction of a tiny glass electrode, 1 μ or less in diameter, into the interior of a single myocardial fiber after piercing its membrane. Such experiments have been successfully carried out on excised cardiac tissues of various species and recently on the beating dog heart in situ. This method permits: (a) direct galvanometric measurement of the polarity and magnitude of potential differences across the cell membrane in its resting state; (b) recording of the magnitude and time course of alterations of these potential differences, when the cardiac cell undergoes excitation, either spontaneously by the propagated cardiac impulse or induced artificially by electric or other extraneous stimuli; (c) correlation of these bioelectric events with the ionic equilibrium and ionic transfer across the membrane during rest and activity; (d) investigation of influences exerted upon membrane resting and action potentials by changes in cellular environments, by nervous influences, and by various drugs; and (e) comparison of the electrophysiologic behavior of skeletal and cardiac muscle, on the one hand, and between specific cardiac fibers and ordinary atrial and ventricular fibers, on the other. Thus, a completely new field has been opened for investigation of cardiac physiology under normal and abnormal conditions, the limits of which cannot be foreseen as yet. Some of the present knowledge gained in this manner is illustrated in diagrammatic form in figures 1 to 3.

Figure 1 shows a schematic diagram correlating the time course of ionic exchange (A) with bioelectric events (B) at the cell membrane during activation and deactivation of a single myocardial (ventricular) fiber, and their temporal relationship to the surface electrogram of the ventricle (C).

In A, the distance between the 2 pointed vertical bars indicates the time during which the tip of a capillary electrode was kept within a ventricular fiber after piercing its membrane, which is represented by the shaded and stippled areas; the former represent the resting state of the fiber, the latter a state of activity engendered by the propagated cardiac impulse. The symbols Na and K indicate accumulation of sodium and potassium ions at respective sides of the resting membrane; their exchange across the membrane during activity is indicated by arrows:

In B, the horizontal line at 0 represents zero potential recorded by a galvanometer connected to a capillary electrode kept at the surface of the cell. Upon piercing of the cell

Fig. 1. Events at the cell membrane during cycle of activation and deactivation of a single myocardial fiber.
membrane a negative deflection of about 100 mv., magnitude is recorded—the membrane resting potential (MRP). MRP remains at a constant (negative) level until the cell is reached by the activation process. The latter is indicated by a rapid reversal of the galvanometric deflection to above zero, the positive overshoot, with subsequent stabilization at zero during the major part of cellular activity. Return to the resting state takes place gradually as indicated by the downward slope of the galvanometric deflection to the negative resting level. The time between positive overshoot and complete return to the resting state represents the duration of the membrane action potential (MAP). From its onset to the beginning of its decline the cell is totally unresponsive to external stimuli—it is in its absolute refractory phase (ARP); during the time of decline of MAP the cell becomes gradually more and more responsive to strong stimuli—it is in its relative refractory phase (RRP).

C represents the QRS and (inverted) T deflection of an unipolar electrogram recorded from the surface of the ventricle simultaneously with MRP.

According to the present state of knowledge the events depicted in A, B, and C appear to be coupled in the following manner: Arrival of the activation process at the cell causes an abrupt change in the permeability of its membrane to sodium and potassium ions. Consequently sodium enters the cell and this causes the almost instantaneous reversal of the negative transmembrane potential (MRP) to a positive overshoot, synchronous with the upstroke of R in the surface electrogram. Subsequent exit of potassium ions from the cell interior abolishes the positive spike and stabilizes MAP at zero levels, 2 events reflected in the surface electrogram as the remainder of the QRS deflection and the isoelectric ST segment respectively. Slow return of potassium ions into the cell signifies restitution of the state of inactivity, the tardiness of the process being reflected in the gradual decline of MAP and the broadness of the T deflection, all this being completed at the same time. Return of sodium ions to the cell surface appears to be accomplished during the resting (“diastolic”) phase of this cycle. The forces that keep potassium ions outside the cell during cellular activity and cause extrusion of sodium ions during the resting period are unknown and are presently ascribed to some active metabolic processes of the membrane itself to which the term “sodium and potassium pumps” have been applied.

In figure 2 are shown membrane resting and action potentials of various types of muscle tissue: (A) dog ventricle, (B) dog atrium, (C) rat diaphragm, (D) Purkinje fiber of the kid. Differences in duration and steepness in the downstroke correspond to differences in the duration of the refractory period of ventricular, atrial, and skeletal muscle. In the Purkinje fiber (D), pacemaker activity is represented by spontaneous recurrence of the positive spike at a rate of 30 per minute. Note that, in contrast to the other muscle fibers (A, B, C), the membrane resting potential does not remain at a constant level but declines from −100 to −60 mv. between successive spikes. This gradual loss of negative charge of the cell interior, referred to as “prepotential,” appears to be characteristic of specific cardiac tissue and is probably related to its pacemaker function. Following treatment by digitalis preparations as demonstrated in the frog heart, the ventricular membrane action potential (A) changes in contour and duration and becomes progressively more like that of atrial and skeletal muscle (B and C).

In figure 3 are listed various factors that act at cellular levels, as demonstrated experimen-
tally by alterations in the shape, duration, and amplitude of the various phases of membrane resting and action potentials (MRP and MAP).

What then is the bearing of this recent progress achieved in the laboratory on the understanding of the variety of digitalis effects in the electrocardiogram? From the information at hand, it is as yet not possible to draw conclusions about mechanisms of the numerous arrhythmias representing the electrocardiographic evidence of therapeutic and toxic actions of digitalis. However, it has been demonstrated conclusively\(^8\) that digitalis preparations produce characteristic alterations in the shape and the duration of the membrane action potential in the frog heart. These alterations appear to be similar, or opposite, to those occurring in membrane action potentials of mammalian papillary muscle or Purkinje tissue subsequent to changes in the ionic concentration of the extracellular fluid, in particular of the K/Ca relationship. On this basis one could expect some differences in the response of the cardiac cell to digitalis, when the latter is applied to preparations surrounded by fluid that is either depleted or enriched in its potassium content. Although experiments designed specifically in this direction have not been reported thus far, it is hoped that a proper evaluation of the digitalis/potassium relationship at cellular levels may provide the basis for a new rationale in the clinical use of the digitalis drugs. Some of the puzzles and hazards associated with digitalis therapy of present days may thus be eliminated in the future.

**Summary**

The various effects of digitalis upon the electrocardiogram are reviewed and grouped with regard to their clinical significance. Therapeutic or toxic actions of digitalis seem to depend on as yet poorly understood relationships to potassium metabolism. An insight into this relationship might be gained in the future in view of recent developments in the field of cardiac electrophysiology.

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